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Neurocognitive basis and treatment of self-blaming emotional biases in major depressive disorder

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**Neurocognitive basis and treatment of
self-blaming emotional biases in
major depressive disorder**

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Abstract

The revised learned helplessness model postulates a critical role for self-blaming biases in the development and perpetuation of clinical symptoms of major depressive disorder (MDD). Causing persistent and excessive feelings of guilt and other self-blaming emotions, a maladaptive attributional style is thought to contribute to depressive symptoms. Current therapeutic approaches are limited in addressing self-blame in MDD, and often patients do not achieve symptom remission or the prevention of recurrent episodes. This is particularly true for MDD patients of the anxious distress subtype.

The work presented in this thesis tested the clinical benefits of a novel self-blame-targeting treatment protocol, employing a self-guided psychological intervention with and without additional real-time functional magnetic resonance imaging (rtfMRI) neurofeedback in early treatment-resistant MDD. Based on the recent finding of guilt-specific hyper-connectivity between the right superior anterior temporal lobe (rSATL) and the posterior subgenual cortex (SC) as a neural signature of recurrence risk in MDD, the single-blind randomised trial presented in this thesis aimed at rebalancing rSATL-SC functional connectivity in MDD, while investigating neurocognitive underpinnings of self-blame. For this purpose, a novel experimental task was developed and tested in anxious and non-anxious MDD patients and healthy control participants.

Both interventions, rtfMRI neurofeedback training and the solely psychological intervention, were found to be safe and therapeutically effective approaches, with response rates of more than 55% in both treatment groups. MDD patients of the anxious distress subtype were found to benefit less from rtfMRI

neurofeedback training and did not present with self-blaming emotional biases compared with non-anxious MDD. Further, despite resulting in a reduction in functional connectivity between the rSATL and the posterior SC, this change was not associated with a reduction in depressive symptoms.

Ultimately, the findings presented in this thesis are only in partial support of the revised learned helplessness model with clearer evidence for its applicability in non-anxious MDD, whereas there was experimental evidence contrary to its predictions in MDD patients of the anxious distress subtype by showing their increased levels of anger directed at others.

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Personal Contribution

This thesis is the result of my own work, in close and active supervision by Dr Roland Zahn and secondary supervision by Professor Steven Williams. Other sources of support are acknowledged by explicit references. The views expressed are my own, guided by the expertise and conceptual input from Dr Roland Zahn.

Chapter I: I undertook all work and writing of this chapter, with conceptual input and feedback provided by Dr Roland Zahn.

Chapter II: Dr Roland Zahn developed the study design and was the principal investigator of the clinical trial presented in this chapter. I contributed to the development of the trial protocol and the application for ethical approval. I was responsible for the recruitment of participants, phone-screening interviews, and conducted all diagnostic assessment and treatment appointments of patients. Dr Roland Zahn was the main assessor of observer-rated clinical outcome measures and supervised my training in assessments using the Structured Clinical Interview for DSM-5. I undertook all statistical analyses, guided and actively supported by Dr Roland Zahn, with additional statistical input from Dr Ewan Carr, a junior statistician, and Dr Kimberley Goldsmith, a senior statistician, at the Biostatistics & Health Informatics Department at the Institute of Psychiatry, Psychology & Neuroscience, King's College London. I undertook all the writing of this chapter, with feedback from Dr Roland Zahn.

Chapter III: I undertook all work and writing of this chapter, with conceptual input and feedback provided by Dr Roland Zahn.

Chapter IV: I undertook all work and writing of this chapter, with conceptual input and feedback provided by Dr Roland Zahn. During the recruitment phase of healthy control participants, a minor number of phone screening interviews was conducted by a postgraduate taught student of Dr Roland Zahn.

Chapter V: I undertook all work and writing of this chapter, with conceptual input and feedback provided by Dr Roland Zahn.

This thesis has been conducted and written in accordance with the PhD programme guidelines of the Institute of Psychiatry, Psychology & Neuroscience, King's College London. It follows a structure that allows each chapter to be read on its own, providing an introduction at the beginning and a reference list at the end of each chapter. Introduction sections of chapters II, III and IV consolidate relevant content presented in chapter I, the main introduction to this work. Further, chapter V captures and discusses the main findings of all previous chapters.

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Abbreviations

ADHD	attention deficit hyperactivity disorder
APA	American Psychiatric Association
ASQ	Attributional Style Questionnaire
BA	Brodmann Area
BDI-II	Beck Depression Inventory-II
BIAT	Brief Implicit Association Test
CBT	cognitive behavioural therapy
CFT	compassion-focused therapy
CI	confidence interval
cLDA	constrained longitudinal data analysis
CPT	cognitive processing therapy
CSQ	Cognitive Style Questionnaire
DAS	Dysfunctional Attitude Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPI	echo-planar imaging
fMRI	functional magnetic resonance imaging
FOV	field of view
FRIEND	Functional Real-time Interactive Endogeneous Neuromodulation and Decoding
GABA	gamma-aminobutyric acid
GAD	generalised anxiety disorder
HAM-A	Hamilton Anxiety Rating Scale
HC	healthy control

HDRS	Hamilton Depression Rating Scale
IAT	Implicit Association Test
IGQ	Interpersonal Guilt Questionnaire
ITT	intention-to-treat
LIFE	Longitudinal Interval Follow-up Interview
M	mean
MADRS	Montgomery-Åsberg Depression Rating Scale
MBCT	mindfulness-based cognitive therapy
MDD	major depressive disorder
MDE	major depressive episode
Mdn	median
PANAS	Positive and Negative Affect Schedule
POMS	Profile of Mood States
PTSD	post-traumatic stress disorder
QUIDS	Quick Inventory of Depressive Symptomatology
ROI	region of interest
rSATL	right superior anterior temporal lobe
rtfMRI	real-time functional magnetic resonance imaging
SAIT	social agency inference task
SC	subgenual cortex
SD	standard deviation
SE	standard error of the mean
SNRI	serotonin-norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
tDCS	transcranial direct current stimulation

TE	echo time
TOSCA	Test of Self-Conscious Affect
TR	repetition time
VMST	value-related moral sentiment task
vs	versus

Chapter I: General introduction

I.1) Background and rationale

I.1.1) Major depressive disorder: the leading cause of ill health worldwide

Depression can affect anyone at any point in life (Friedrich, 2017). Major depressive disorder (MDD) has been recognised to be a serious mental health condition, describing an affective syndrome distinct from normal sadness or occasional low mood (Holtzheimer & Mayberg, 2011; Schulz & Arora, 2015). Depression is declared to be the leading cause of ill health and disability worldwide and is proposed to become the primary contributor to the global burden of disease by 2030 (World Health Organization, 2008, 2017). Highly debilitating in nature, depression has a profound negative impact on the quality of life of those affected.

In MDD, a complex cluster of clinical symptoms constrains the individual's everyday well-being and is displayed to different extents and in various severities among patients. Nevertheless, core symptom features of MDD are a state of severe despondency and anergia (Holtzheimer & Mayberg, 2011). According to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association [APA], 2013) at least five of the following symptoms need to be present nearly every day over a duration of a two-week period in order to fulfil clinical criteria for MDD: 1) depressed mood and/or anhedonia (loss of interest or pleasure), 2) >5% weight loss or weight gain or a decrease or increase in appetite, 3) psychomotor agitation or retardation, 4) insomnia or hypersomnia, 5) fatigue or loss of energy, 6) feelings of worthlessness or excessive, inappropriate guilt (not merely self-

reproach or guilt for being sick), 7) diminished concentration, and 8) recurrent thoughts of death (not just fear of dying) or suicidal ideation. Only if the symptoms result in the significant impairment of one's psychosocial functioning, and are not evoked by substance use or a physical health condition (e.g. hypothyroidism), a diagnosis of MDD is given.

To this date, a plethora of research has been conducted in an attempt to decipher the complexity of this mood disorder and unveil the causal basis of its clinical presentation. Nevertheless, despite the development of a variety of pharmacological and psychological treatment options, a majority of MDD patients experience the current standard of available interventions as only partially effective in the long run (Bockting et al., 2009; Viguera, Baldessarini, & Friedberg, 1998) or never entirely remit from their major depressive episode (MDE) despite receiving standard treatment (Nierenberg & Amsterdam, 1990; Rush et al., 2006). Also, patients who experience at least two MDEs are found at increased risk of developing further episodes in the future (Eaton et al., 2008). However, all research efforts so far have failed to conclude irrefutably on the causal origin of MDD and to establish interventional approaches that not only temporarily stabilise the patients' condition but prevent a lifelong recurrence. Novel interventions are needed, effectively addressing depressive symptomatology and the vulnerability for developing MDD.

I.1.2) The role of self-blaming biases in psychological models of MDD

In his work on 'Mourning and Melancholia', Freud (1917, 1924) posits the theory that it is the presence of self-blaming emotions that distinguish the pathological state of depression from adaptive sadness and healthy mourning. He

claims that ambivalence with the departed can turn unconscious anger towards others inwards, ultimately resulting in self-directed anger. Thus, opposed to the experience of grieving, depression is thought to be associated with a critical judgement of the ego due to the perception of having failed to live up to ideals (Freud, 1917, 1924). Freud further suggests that in a depressive state, the ego is being attacked by repressed emotions towards the deceased individual (Freud, 1917, 1924). The depressed individual reproaches himself and expects to be punished (Freud, 1917). This causes the ego to divide into two parts that rage against each other, whereby one part comprises an inexorably critical component within the ego (Carhart-Harris, Mayberg, Malizia, & Nutt, 2008; Freud, 1917).

Similar to Freud, Beck (1967) regards self-blame as a primary feature of depression, occurring in 80% of severely depressed patients opposed to 43% of non-depressed individuals. Contrary to Freud, however, Beck posits that self-blaming emotions arise due to a tendency to take responsibility for negative outcomes of events (Beck, 1963). Specifically, Beck (1963) suggests that depressive affect may develop secondary to the presence of distorted cognitive conceptualisations, although reciprocal interactions between cognition and affect are possible. He acknowledges the presence of self-criticism (i.e. self-condemnation) as a prominent clinical feature amongst patients with depression compared to a non-depressed cohort and explains self-criticism as a self-directed reproach for perceived weaknesses (Beck, 1963). Whelton & Greenberg (2005) link pathogenic self-criticism to self-directed anger, self-disgust and self-contempt.

Self-criticism is considered a personality disposition and vulnerability factor for feelings of guilt and self-blame, predictive of depression (Manfredi et al., 2016; Werner et al., 2019) and different models attempt to explain its origin. Self-criticism is posited to be the result of a deviation in personality development (Blatt, D’Afflitti & Quinlan, 1976; Blatt & Zuroff, 1992) or to be triggered by negative experiences within the motivational system for competition and social rank, provoked by a lack of self-defence mechanisms (e.g. self-reassurance) (Gilbert et al., 2006). Other approaches suggest parental criticism during childhood expressed verbally and through critical emotions to be a causal factor of depressogenic self-criticism (Shahar, 2015) and associated with self-blaming tendencies in children (Jaenicke et al., 1987; Rubenstein et al., 2016).

Beck (1963) proposes that self-blaming emotions might be arising due to a dysfunctional (overgeneralised) self-critical attitude, separate from low self-evaluation. The author further stresses the observation that no logical basis underpins self-blaming tendencies in MDD, as they may be caused by an erroneous interpretation of reality (Beck, 1963). Beck concludes that depression is characterised by the presence of the ‘cognitive triad’ of automatic negative thinking, comprised of 1) a negative, i.e. critical view of the self, missing attributes necessary for success, 2) a negative interpretation of current experiences, anticipating negative outcomes from any undertaking and thirdly, 3) a negative view of the future. According to Beck’s theory, such automatised self-directed negative thought processes and interpretations result from depressogenic self-schemata grounded in negative experiences during childhood that led to biases in the perception of the self and self-related information (Beck et al., 1967).

Analogous to Beck (1963), Abramson, Seligman & Teasdale (1978) postulate that a distinct cognitive attributional style predisposes individuals to depression. The authors introduce the revised learned helplessness model and suggest that attributions are principal in determining affect (Abramson et al., 1978). According to this appraisal theory, the individual's causal attribution of a negative event determines how they feel about the situation and its consequences. Causal attributions to a negative event can occur on three dimensions: 1) either internal or external, involving the individual personally or the event itself, 2) may be perceived as persistent or transient in regard to time, and 3) may be viewed as global or specific, i.e. impacting negatively on manifold outcomes or being limited to that one negative event (Abramson et al., 1978). Internal attribution of causality for a negative event may result in low self-esteem; stable causal attribution is thought to be associated with persistence of chronicity of depression, as is a persistent attribution of cause (Abramson et al., 1978). Thus, individuals who display internal, stable and global attributions of negative causation are thought to be highly vulnerable to developing depression when confronted with negative events beyond their control (Hoffman & Al'Absi, 1998).

Ultimately, in this model, depression vulnerability is thought to arise as a consequence of the presence of motivational, cognitive and affective deficits as well as deficits in self-esteem. Whereas motivation, cognition and self-esteem are understood as being based on uncontrollability, i.e. the thought to arise as a consequence of learning that the outcome is uncontrollable, affective deficits are assumed to arise due to the general belief that negative outcomes will occur (Abramson et al., 1978). To summarise, the revised learned helplessness model states that overgeneralised self-blame leads to increased feelings of guilt and in

turn to low self-worth, which corresponds to a high-level vulnerability for depression.

Teasdale (1983) points to a bi-directional reciprocal relationship between emotions and cognition in depression, stressing the possibility that not only negative thinking may lead to or maintain depressed mood, but that depressed mood may also be the cause of negative thinking biases. Contrary to Beck, however, Teasdale claims that dysfunctional attitudes are not always observed in individuals remitted from depression (Lau, Segal, & Williams, 2004). Teasdale, therefore, contradicts Beck's postulation that dysfunctional attitudes are necessarily a vulnerability factor for depression. He proposes the differential activation hypothesis to explain cognitive vulnerability to depression and declares cognitive reactivity to be crucial in determining depression severity and persistence (Teasdale, 1983, 1988). Further, he postulates that depressogenic cognitions (i.e. negative information processing biases) are triggered by dysphoric mood states, a theory that was supported by his research on mood priming and the subsequent assessment of dysfunctional attitudes in MDD (Lau et al., 2004; Teasdale, 1983, 1988).

By no means does this brief overview on psychological theories of MDD claim completeness, yet it aims at demonstrating that all these influential MDD models agree on an essential role of self-blame (biases) and associated emotions in the pathogenesis of depression.

Furthermore, the social model of MDD postulated by Brown & Harris (1978) assumes a key role for psychological factors such as low self-esteem in the

mediation of the relationship between stressful life events and depression. Notably, as aforementioned, low self-esteem is a result of cognitive self-blaming biases, according to Abramson et al. (1978). Recent experimental evidence in MDD demonstrated that patients with MDD are further affected by a negative memory bias, ultimately, resulting in generalised biases towards negative self-judgement (Hitchcock, Rees & Dalgeish, 2017).

The widely formulated consensus on a central role of self-blaming emotions in MDD is in contrast to another influential model that postulates decreased positive and increased negative emotionality in MDD (Watson, Clark, & Carey, 1988a). Using a measure of positive and negative affect, the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988b), the authors investigated individuals diagnosed with anxiety or depressive disorders and found that both patient groups showed increased negative emotions, yet a significant reduction of positive emotions was distinctive for MDD (Watson et al., 1988a; Watson et al., 1988b). Recent papers in remitted MDD, however, contradict the predictions of this model by use of the value-related moral sentiment task (VMST; Zahn et al., 2009b), showing a reduced level of negative emotions towards others (contempt/disgust and indignation/anger towards others) and a relative increase in overgeneralised self-blaming emotions, e.g. self-contempt bias (Green, Moll, Deakin, Hulleman, & Zahn, 2013; Zahn et al., 2015b).

Despite a strong theoretical case for the importance of self-blaming emotions in MDD, as outlined above, the evidence base so far is inconsistent.

Research using the Attributional Style Questionnaire (ASQ; Peterson et al., 1982) failed to show replicable evidence of self-blaming attributional styles in individuals vulnerable to MDD (Green et al., 2013). One reason for this might be that the ASQ uses hypothetical scenarios which are of different relevance to different participants. Also, the ASQ does not ask the participant about the emotional relevance of their attribution. Furthermore, it needs to be considered that self-blaming emotional biases found with the VMST have so far not been probed in symptomatic MDD. In addition, unpublished secondary data analyses of the data in Zahn et al. (2015b) point to self-blaming emotional biases being more pronounced in melancholic subtype patients. This finding calls into question whether these biases can be detected across a broader range of patients, including those resistant to full remission as seen in specialist clinics who often fall into the anxious distress subcategory of MDD (Fava et al., 2008; Gaspersz et al., 2017).

In this thesis, I will assume a strong relationship between self-blaming emotions and cognitions that cannot be dissociated. This view is based on a neurocognitive model of complex socio-moral emotions and cognitions that presumes overlapping neural and cognitive elements of socio-moral cognition and emotion (Moll, De Oliveira-Souza, & Zahn, 2008; Moll, Zahn, de Oliveira-Souza, Krueger, & Grafman, 2005). Specifications of this model are further explained in the following section of this chapter. This view is also in keeping with the differential activation hypothesis, which assumes a bi-directional and close relationship between emotions and cognitions (Teasdale, 1988).

I.1.3) Self-blaming emotional biases and moral motivation

Morality is understood as a set of values that are adopted by a cultural group and directive of social conduct (Moll et al., 2005). The term ‘moral motivation’ was coined by Francis Hutcheson, who postulated that actions and behaviours are motivated by moral sense (Bishop, 1996). According to this theory, moral sense, in turn, gives rise to pleasure or pain, both forms of desire, and thereby driving behaviour (Bishop, 1996). According to Hutcheson’s theory, moral sense can motivate action, but it is benevolence that motivates virtuous acts (Bishop, 1996). Contrary to Hutcheson’s view on moral sense, his successor Adam Smith claimed, that it is not self-interest, but ‘moral sentiments’, sympathy, in particular, that constitute the root source for moral motivation (Lamb, 1974). Zahn, De Oliveira-Souza & Moll (2018a) remark that it is the motivation that drives the action, which distinguishes cognitive and emotional components underpinning moral behaviour compared with social behaviour in general.

Moll and colleagues define moral sentiments, feelings or emotions as complex subjective experiences that enable humans to be motivated by the needs of other individuals or directed by sociocultural norms (Moll et al., 2008, Zahn, De Oliveira-Souza, & Moll, 2013; Zahn, De Oliveira-Souza & Moll, 2011). Also, modern psychologists classify various feelings related to self-blame as ‘moral emotions’, i.e. guilt (O’Connor, Berry, & Weiss, 1999; Tangney, 1991), shame (Tangney, 1991), self-directed anger (Freud, 1917, 1924), and self-directed contempt/disgust (Green et al., 2013). Further, feelings related to blaming others, such as moral disgust/contempt and indignation/moral anger towards others are considered moral emotions (Moll et al., 2007).

Evolutionary simulation models showed that moral emotions related to blaming others, such as indignation towards others, are crucial determinants in the enforcement of moral rules in societies by enabling so-called altruistic punishment (Fehr & Fischbacher, 2003). Notably, altruistic punishment describes the instance when individuals risk their resources or health to punish people who act against the common welfare (Fehr & Gächter, 2002). Blaming others is also known as a defence mechanism in order to protect one's self-esteem (Bentall, Kinderman, & Kaney, 1994; Lyon, Kaney, & Bentall, 1994). Thus, one would expect that self-esteem and moral motivation critically depend on the balance between emotions related to self-directed blame and blaming others.

I.1.4) The neural basis of self-blaming emotional biases in MDD

The neural basis of affect is proven to be complex, even if emotions are experienced as distinct feelings (Kragel & LaBar, 2016). Different views have been expressed in the attempt to conclude whether representations of emotions in the brain involve discrete neural circuits for specific emotions (Hamann, 2012; Kragel & LaBar, 2014) or whether the brain basis of emotions consists of an integrated system underpinning all emotions (Barrett, 2006; Lindquist et al., 2012). While two-dimensional models (implicating pleasure and arousal) have been shown to be applicable to the experience of emotion (Russel, 1980), they fail to explain why brain injury or mental illness can result in selective emotional impairment (e.g. the recognition of disgust) instead of causing damage to a broader scope of emotions (Calder, Lawrence & Young 2001). Neuroimaging studies implementing multivoxel pattern analysis provide further evidence against dimensional theories and support the notion that neural systems underlying

emotion categories can be discriminated despite relying on distributed cortical and subcortical brain regions (Kragel & LaBar, 2016).

Using functional magnetic resonance imaging (fMRI) and an earlier version of the VMST, Zahn et al. (2009b) investigated the neural basis of context-dependent moral sentiments in healthy control (HC) participants. Amongst other sentiments, such as pride and gratitude, the authors were particularly interested in exploring the neural architecture of guilt, employed in a negative self-agency condition, and indignation/anger, evoked in a negative other-agency condition. Activation in the right superior anterior temporal lobe (rSATL; Brodmann Area [BA] 38/22) was independent of agency and valence, and activation in this area was significantly associated with the level of descriptiveness of the social behaviour investigated. This finding confirmed previous results by the authors, who concluded that the rSATL represents conceptual knowledge that allows the comprehension and evaluation of social behaviours (Zahn et al., 2007). Specific to the guilt condition, but not the indignation/anger condition in the fMRI experiment, was activation in the ventromedial prefrontal cortex (which was also found for pride). Activity in the subgenual cingulate, however, was only found to be a correlate for guilt (Zahn et al., 2009b). Conversely, feelings of anger/indignation towards others correlated with activity in the lateral orbitofrontal-insular cortices (Zahn et al., 2009b).

In another study in HC participants (Zahn, de Oliveira-Souza, Bramati, Garrido, & Moll, 2009a), the same research group confirmed the link between subgenual activity and feelings of guilt. It is noteworthy, however, that in both studies (Zahn, De Oliveira-Souza, et al., 2009a; Zahn, Moll, et al., 2009b), the subgenual region was only associated with guilt, when individual differences were

modelled for either proneness to guilt (Zahn, Moll, et al., 2009b) or empathic concern (Zahn, De Oliveira-Souza, et al., 2009a). Zahn et al. (2018a) concluded from these findings that the role the subgenual area plays in the experience of guilt might depend on proneness to guilt or empathic concern.

Further, Moll et al. (2011) investigated prosocial sentiments, including guilt, pity and embarrassment, using a moral sentiment test in patients diagnosed with frontotemporal dementia. This research built on previous observations of inappropriate and less prosocial behaviour in individuals with lesions to the frontopolar and ventromedial frontal areas (Liu et al., 2004; Zahn, 2015a). Using 18-Fluoro-Deoxy-Glucose-Positron Emission Tomography to assess participants' regional cerebral glucose metabolism (Herholz, Carter & Jones, 2007), Moll et al. (2011) found that the degree of impairment of prosocial sentiments (guilt, pity and embarrassment) was linked with the degree of abnormalities of glucose metabolism in the frontopolar cortex, whereas the loss of feeling of guilt and pity was linked to septal dysfunction. Other-blaming emotions, e.g. anger or disgust towards others, were associated with abnormal glucose metabolism in the dorsomedial prefrontal cortex and the amygdala.

Frontopolar activations were also associated with guilt compared with other unpleasant emotions in fMRI studies of HC populations (Basile et al., 2011; Moll et al., 2007; Morey et al., 2012) as further summarised in Zahn et al. (2018a).

Zahn and Moll's research findings of subgenual and adjacent septal activation in relation to guilt compared with indignation were complemented by research demonstrating subgenual activation in a charitable donation task in HC

participants (Moll et al., 2006) and replicated in remitted MDD for the first time by Green, Lambon Ralph, Moll, Deakin & Zahn (2012).

Green et al. (2012) were interested in investigating the neural architecture of self-blaming biases in MDD. Comparing a remitted MDD group with HC participants, the authors investigated whether the MDD group would show guilt-selective connectivity abnormalities between the subgenual cingulate cortex/septal region and the rSATL as a marker of deficient functional integration, which could explain overgeneralised self-blaming biases in MDD. The hypothesis was based on fMRI evidence of functional integration between the rSATL and the subgenual cingulate region during the experience of guilt in HC participants. This signature was specific to guilt, contrary to a functional integration pattern of the rSATL with the lateral orbitofrontal cortex for indignation in HC participants (Green et al., 2010). In their investigation in remitted MDD, Green et al. (2012) recruited an MDD group that was medication-free, in remission for more than one year and comparable with HC participants regarding psychosocial functioning and depression scores (within a normal range). All participants underwent fMRI and completed the VMST post-scanning and were assessed for overgeneralised self-blame by means of the validated Interpersonal Guilt Questionnaire (IGQ; O'Connor, Berry, Weiss, Bush & Sampson, 1997). In their analyses, the authors controlled for the degree of negative valence and emotional intensity. As predicted, a guilt-selective decrease in connectivity between the rSATL and the subgenual/septal region was found compared with HC participants. In addition, connectivity between the rSATL and other brain regions was found, including medial frontopolar, right hippocampal and lateral hypothalamic areas (Green et al., 2012). The authors concluded from their findings that temporofrontolimbic

connectivity abnormalities underpin self-blaming emotional biases in (remitted) MDD and are associated with an increased vulnerability to depression.

Further evidence for the neural basis of self-blaming emotions in remitted MDD was provided by Lythe et al. (2015). This study found self-blame to be associated with a selective hyper-connectivity pattern (relative to blaming others) between the rSATL and the posterior subgenual cortex (SC; BA 25) in those remitted from MDD who would develop another episode of MDD within 14 months. The predictive accuracy was estimated at 75% (Lythe et al., 2015). The recurring MDD group was found to show significantly higher connectivity between these brain areas than the stable group and HC participants. The difference in the direction of self-blame-selective connectivity abnormalities in MDD between the studies by Lythe et al. (2015) and Green et al. (2012) is suspected of having occurred by differences in clinical features in both patient samples (Lythe et al., 2015). Specifically, in their prospective study, Lythe et al., (2015) report a significantly higher overall risk of recurrence, with only 23% of MDD patients having experienced only one previous MDE. On the contrary, Green et al. (2012) base the findings of their cross-sectional study on a sample comprised of MDD patients with a lower overall recurrence risk, with 56% of MDD patients having had only one MDE prior to study participation.

A systematic review on the neurobiology of shame and guilt, comprising 21 studies, including studies in remitted MDD, further highlights activations in the ventral anterior cingulate cortex, posterior temporal regions and precuneus for guilt and activity in the dorsolateral prefrontal cortex, posterior cingulate cortex and sensorimotor cortex for shame (Bastin, Harrison, Davey, Moll, & Whittle,

2016). Moreover, quantitative meta-analyses were published on the neural basis of guilt, e.g. Gifuni, Kendal & Jollant (2017) and are in partial support of the findings by Zahn and Moll as presented above. Nevertheless, Zahn et al. (2018a) stress methodological, appraisal and reporting issues of these reviewing studies (Bastin et al., 2016; Gifuni et al., 2017) which impede clear conclusions. As these reviews miss to stress subgenual/septal activation during the experience of guilt, Zahn et al., (2018a) remark that the focus of the studies included was not on controlling for individual differences in the experience of guilt-evoking stimuli or on employing optimised sequences for ventral frontal regions.

To summarise, the literature on the neural basis of self-blame in HC participants and patients with frontotemporal dementia points to the importance of the frontopolar and subgenual cingulate cortices (extending posteriorly to the adjacent septal area) when compared against indignation towards others or other unpleasant emotions. Zahn et al. (2018a) provide an extensive summary of the current literature. Subgenual cingulate activations are only reproducible when individual differences in guilt proneness or empathic concern are modelled. These findings have been replicated in remitted MDD, with research in current MDD lacking. Lythe et al.'s study (2015) further emphasises the impact of self-blaming emotions and their rSATL-subgenual associated neural signature in MDD, even during phases of remission. Moreover, these findings stress the necessity to target self-blaming biases in MDD with effective interventional strategies to decrease MDD vulnerability and prevent recurrence risk in this population.

I.1.5) Treatment of self-blaming emotional biases in MDD

Cognitive therapy has been proven considerably successful in the treatment of depression (Strunk & De Rubeis, 2001), however, to my knowledge, its therapeutic effectiveness in tackling self-blaming emotions in depression specifically has not been investigated. This is if one assumes that the Dysfunctional Attitude Scale (DAS; Weissman & Beck, 1978), designed to capture treatment targets for cognitive therapy, measures more than just self-critical/self-blaming emotions.

Some research exists on treating self-blame in post-traumatic stress disorder (PTSD), whereby cognitive processing therapy (CPT) is used, which was adapted from techniques from cognitive therapy and developed specifically for PTSD resulting from sexual assault (Resick & Schnicke, 1992). Implementing Socratic questioning, CPT has been found effective in the treatment of self-blame, i.e. guilt in PTSD (Resick, Nishith, Weaver, Astin, & Feuer, 2002) by focussing on distorted beliefs, including self-blame and overgeneralised beliefs about oneself and the world (Resick et al., 2002).

Socratic questioning is also a key therapeutic strategy in cognitive therapy for depression (Beck, Rush, Shaw & Emery, 1979), and aims at deconstructing dysfunctional beliefs and assumptions by the use of therapist-guided, goal-directed, open-ended questions that encourage the patient to develop new perspectives and integrate new information (Beck et. al., 1979; Rutter & Friedberg, 1999). Thereby, alternative responses to automatic negative thought processes are meant to be developed (Beck et al., 1979). Research on Socratic questioning in relation to treatment outcome is sparse, yet it was found to be predictive of a session-to-session decrease in depressive symptomatology in MDD

(Braun, Strunk, Sasso, & Cooper, 2015). However, as aforementioned, cognitive therapy, and Socratic questioning as such, do not focus on self-blaming emotions in depression *per se*.

Attribution retraining is a therapeutic technique central to cognitive behavioural therapy (CBT) (Hilt, 2004; Laird & Metalsky, 2009). Besides being used in social skills training in school-based interventions (Carlyon, 1997), it finds its application across a variety of mental health disorders in adults (Forsterling, 1985; Metalsky et al., 1995), including MDD (Wang et al., 2011). Importantly, therapeutic attribution retraining for depression is found to be contraindicated for individuals diagnosed with depression who find themselves in an acute state of psychosis (Laird & Metalsky, 2009). Furthermore, attributional retraining is suggested to be less effective if dysfunctional attributional styles have been exerted for prolonged periods (Crick & Dodge, 1994).

Attribution retraining is designed to increase the individuals' ability to notice and critically assess their dysfunctional attribution patterns and to actively shift their focus on developing a more adaptive attributional style instead (Forsterling, 1985; Hilt, 2004). Critical therapeutic steps in the attempt to help patients with MDD change their dysfunctional attributions is the examination of the evidence for and against the individual's depressogenic attributions. The therapist may challenge the individual's biased thinking patterns by exploring whether blame and responsibility for causing a specific adverse event are truly absolute. Further techniques involve asking the patient if they would make similar attributions if someone other than themselves would be in the same situation (Laird & Metalsky, 2009). Following the practice of retraining attributions for

specific situations, the patient is then encouraged to generalise this more realistic, adaptive thinking pattern in their evaluation of other negative life events (Laird & Metalsky, 2009).

Being implemented as a substantial component of CBT, attribution retraining has been shown to be beneficial for patients with MDD in reducing symptoms of depression (Laird & Metalsky, 2009). However, only a few studies exist investigating the efficacy of attributional retraining independent of its CBT context. Hilt (2004) concludes that treatment outcome research remains poor regarding CBT-independent attribution retraining in adults. Wang et al. (2011) conducted a pilot study testing the therapeutic effect of attribution retraining in a group setting and found this technique to be beneficial in the improvement of feelings of hopelessness and well-being in MDD, the effect of attributional retraining on self-blaming emotions, however, was not assessed.

A more recent therapeutic approach, compassion-focused therapy (CFT) integrates scientifically based models, including CBT with mindfulness and Buddhist teachings (Gilbert, 2009a, 2009b). It targets feelings of self-criticism explicitly as one of its central components. Therefore, CFT was initially developed for individuals who present with high levels of self-criticism and shame, as often observed in MDD, its application, however, is extended to other mood and anxiety disorders and beyond. CFT teaches patients to feel compassionate towards themselves and to be accepting and kindly tolerant of distress in self and others. Specifically, patients are practising to detect self-criticism in their thought processes and are then instructed to refocus with self-kindness by generating and practising compassionate feelings and thoughts that

are supportive and encouraging in nature (Gilbert, 2009a, 2009b). As a final step in this process, patients are helped to become aware of how this compassionate shift has positively helped them in their mental and emotional state.

CFT is found to be an effective intervention in the treatment of self-criticism and depressive symptoms across different groups of disorders and populations (Cuppige, Baird, Gibson, Booth, & Hevey, 2018). A systematic review by Leaviss & Uttley (2015) evaluated the clinical benefits of CFT as a psychotherapeutic intervention and confirmed that CFT shows promise in the treatment of mood disorders, particularly in patients with high levels of self-criticism. It is noteworthy, however, that this review did not primarily focus on MDD, and studies varied profoundly in their treatment protocol. Furthermore, only three of the 14 studies included consisted of a randomised controlled study design. To conclude from the present state of research, more studies are needed, utilising a robust methodology to assess the effectiveness of CFT in targeting self-blame specifically in MDD.

I.1.6) Real-time fMRI neurofeedback as a novel approach to tackling self-blaming emotional biases in MDD

Real-time fMRI (rtfMRI) neurofeedback is a rather novel, investigational approach in the line of pharmaco-independent neuromodulation treatments in MDD. It aims at exploring the causal relationship between targeted brain functions and resultant behavioural changes (Sitaram et al., 2017; Watanabe, Sasaki, Shibata & Kawato, 2017). This method provides near real-time information about changes in neural activity, thereby facilitating the individual to execute self-regulation of brain function, cognition and behaviour (Stoeckel et al.,

2014; Thibault, Lifshitz, & Raz, 2016). Notably, it is based on measuring changes in neurovascular coupling and provides, therefore, only an indirect measure of neural activity (Linden, 2014). Research has demonstrated that rtfMRI enables individuals to gain voluntary control over the activity and connectivity of brain regions (Sulzer et al., 2013; Weiskopf, 2012) and has been shown to have positive clinical effects in various clinical populations, including psychiatric conditions, e.g. schizophrenia (Ruiz et al., 2013) and PTSD (Misaki et al., 2018; Zotev et al., 2018), neurological disorders, e.g. stroke (Sitaram et al., 2012), as well as chronic pain (deCharms et al., 2005) and chronic tinnitus (Haller, Birbaumer, & Veit, 2010).

To this date, research on rtMRI neurofeedback in depression is still in its early stages (Young et al., 2017a; Young et al., 2018a; Young et al., 2018b; Yuan et al., 2014; Zotev, Phillips, Yuan, Misaki, & Bodurka, 2014; Zotev et al., 2016), even fewer studies have focused on investigating the clinical benefits of rtfMRI neurofeedback in MDD (Linden et al., 2012; Mehler et al., 2018; Young et al., 2017b; Young et al., 2014), one review was published on the promise of amygdala-focused rtfMRI in MDD (Young et al., 2018b).

Pioneering in exploring the application of rtfMRI neurofeedback as a therapeutic tool in MDD was a proof-of-concept study conducted by Linden et al. (2012). The authors applied four sessions of rtfMRI neurofeedback in a non-randomised trial against a control intervention. The rtfMRI neurofeedback intervention sessions were stretched over a duration of 4-6 weeks and targeted a small sample of MDD patients (n=8) who were stable on antidepressant medication with no positive change in symptoms over the past six weeks prior to

participating in the study. In the rtfMRI neurofeedback group, target regions of interest (ROIs) were identified for each participant separately, using a localiser procedure that detected networks responsive to positive images, i.e. the ventrolateral prefrontal cortex and insula. Participants were trained in the upregulation of these specific brain regions associated with positive mood by the use of cognitive strategies. Similarly, the control group employed the same positive imagery strategies outside the fMRI scanner and without receiving rtfMRI neurofeedback. Among other clinical measures, improvement in depressive symptoms was assessed by means of the 17-item Hamilton Depression Rating Scale (HDRS-17) and MDD patients undergoing rtfMRI neurofeedback training were found to significantly reduce their depression scores by the end of the study compared to no significant reductions in symptoms in the control group (Linden et al., 2012).

In a more recent study by the same research group (Mehler et al., 2018), the authors employed a single-blind, randomised controlled trial design, comparing the clinical benefits of rtfMRI neurofeedback in the upregulation of emotion areas (functional localiser, including limbic and frontal parts of the anterior telencephalon) with the upregulation of a control region implicated in mental imagery of visual scenes (i.e. parahippocampal place area). Target areas in both intervention groups were expected to be comparable in upregulation success and hence, in reward experience. Five interventions were appointed to each patient group, and the outcome assessed after 12 weeks post-baseline. Patients were on stable antidepressant medication for at least three months; ongoing non-pharmacological treatment was excluded. Participants' depression symptoms were evaluated by a blinded assessor using the HDRS-17; ultimately, data of 16

completers in each group was analysed. A symptom reduction of 43% was recorded, interestingly, no group differences in depressive symptom reduction occurred between active and control group. Also, no differences were found in the upregulation of target areas. It is noteworthy that clinical improvements remained stable at a follow-up assessment six weeks post-outcome assessment. The authors reported that their results outweighed placebo effects reported in other intervention studies and concluded that the experience of success in the upregulation of brain areas during rtfMRI neurofeedback training might account for the reduction in depressive symptoms in both groups, rather than the specific targeting of emotion-regulation areas (Mehler et al., 2018).

Replicated support for the clinical benefits of rtfMRI neurofeedback in depressive populations has been provided by research targeting amygdala activation in MDD (Young et al., 2017b; Young et al., 2014). Young et al. (2017b) conducted the first double-blind randomised-controlled clinical trial investigating the clinical efficacy of rtfMRI neurofeedback in MDD, subsequent to delivering promising findings in a non-randomised study in a moderately sized sample of MDD patients (Young et al., 2014). This research group addressed the reduced hemodynamic amygdala activation in response to positive autobiographical stimuli (e.g. pleasant memories) in MDD by successfully training patients in rtfMRI amygdala neurofeedback. Results of two sessions of left amygdala enhancing rtfMRI neurofeedback during the retrieval of autobiographical memories were compared with the outcome of a control condition that employed two sessions of activating rtfMRI neurofeedback

targeting parietal brain regions not involved in emotional processing, i.e. the left intraparietal sulcus.

All MDD patients (n=36) were medication-free, with the majority of patients suffering from chronic MDD and half of the patient group had been treated with antidepressant medication at some point in their lives. Anxiety disorders were no exclusion criterion in this trial and patients scored in the moderate anxiety range as assessed with the Hamilton Anxiety Rating Scale (HAM-A). The primary outcome measure constituted of the reduction in symptom scores on the Montgomery-Åsberg Depression Rating Scale (MADRS). The authors reported comparable success rates in the upregulation of target areas between groups, however, only the amygdala neurofeedback group was found to show a response rate of 63%, marking a reduction in depressive symptomatology by at least 50% compared to a 12% response rate in the control condition (Young et al., 2017b).

A recently completed, double-blindly randomised proof of concept trial in MDD employed rtfMRI neurofeedback targeted at reducing self-blaming emotions in 28 patients with remitted MDD (Zahn et al., 2018b). Based on previous findings of guilt-selective connectivity decreases between the rSATL and the anterior subgenual cingulate cortex (Green et al., 2012), as outlined in section I.1.3 within this chapter, the rtfMRI neurofeedback intervention in the active condition was targeted at increasing rSATL–subgenual cingulate cortex connectivity during the experience of feelings of guilt compared with indignation. MDD patients received a single session of rtfMRI neurofeedback. Feelings of guilt and anger were evoked using autobiographical memories during the experiment. MDD patients were instructed to feel the emotion while trying to

enhance the brain connectivity pattern that was fed back to them using a thermometer-like display (Zahn et al., 2018b).

MDD patients were found to be successful in increasing connectivity levels between the rSATL and the anterior subgenual cingulate cortex (BA 24). Moreover, a significant improvement in self-esteem was recorded, as assessed with the Rosenberg Self-esteem Scale. These findings differed significantly from the control intervention who received neurofeedback during the experiment that reinforced a stabilisation of baseline connectivity patterns instead of reinforcing an enhancement as in the active condition. This study was the first to show that, self-blame selective abnormal connectivity patterns can be targeted by rtfMRI neurofeedback in remitted MDD. Further, it confirmed the hypothesis that the abnormality of this connectivity pattern is crucial in compromised levels of self-esteem in MDD (Zahn et al., 2018b).

I.1.7) Gap of knowledge

Real-time fMRI neurofeedback is found to be a non-invasive tool with potential clinical benefits in MDD, showing positive effects in targeting emotion-related brain regions in current and remitted MDD, as an add-on treatment to stable antidepressant medication as well as an alternative intervention strategy in medication-free MDD. So far, only one study has tested the feasibility of rtfMRI neurofeedback targeting self-blame-selective neural connectivity abnormalities as demonstrated to be present in remitted MDD (Zahn et al., 2018b). Based on the current literature it remains unclear, however, whether self-blame-selective rtfMRI neurofeedback will show clinical potential in early treatment-resistant MDD, as the previous trial focussed primarily on remitted MDD and was

designed as a technical proof-of-concept study rather than investigating clinical outcomes (Zahn et al., 2018b).

Guilt-selective hyper-connectivity between the rSATL and posterior subgenual cingulate cortex (BA 25) has been shown to be predictive of recurrence risk in MDD. It is unknown to this date if self-blame selective posterior subgenual–anterior temporal hyper-connectivity can be successfully tackled using rtfMRI neurofeedback training, and whether a successful normalisation in abnormal connectivity patterns corresponds to an overall improvement in depressive symptoms, alongside a reduction in self-blaming emotional biases and a significant increase in measures of self-esteem.

To address the substantial need for research investigating these critical questions, this PhD project aimed at exploring the neurocognitive basis of self-blaming emotional basis in MDD further. This work developed a particular focus on investigating the feasibility and clinical benefits of a self-guided psychological intervention with and without additional rtfMRI neurofeedback training and tackling self-blame-selective posterior subgenual–anterior temporal hyper-connectivity in early treatment-resistant MDD. These research endeavours are particularly important when considering the adverse impact of self-blaming emotional biases in MDD, the lack of interventions explicitly targeting self-blame in MDD and the urgent need for novel interventions as a high number of MDD patients only insufficiently respond to standard pharmaco-therapy or psychotherapeutic treatments.

Finally, it is noteworthy, that current studies investigating self-blaming emotional biases or rtfMRI neurofeedback intervention strategies in MDD have not explored potential differences between subtypes of depression. A highly

prominent subtype of MDD, particularly in treatment-resistant patients, is the anxious distress MDD subtype as classified according to the recently introduced DSM-5 diagnostic criteria. Explicit research on this common subtype is still sparse, however, important prognostic differences between MDD with and without anxious distress symptoms have been reported in the literature, e.g. in treatment response, which points to the possibility of a different neurocognitive signature underpinning these subtypes and the necessity for different interventional approaches in MDD with anxious distress compared with non-anxious MDD.

I.1.8) General aims and hypotheses

The research conducted and presented in this thesis aims at contributing to previous research findings that have highlighted the importance of acquiring a better understanding of the neurocognitive basis of self-blaming emotional biases in MDD. It further aims at testing the feasibility and initial evidence of the clinical potential of rtfMRI neurofeedback training compared with a solely self-guided psychological intervention tackling self-blaming emotional biases in early treatment-resistant MDD. Further, this thesis investigates differences in the neurocognitive architecture of self-blaming emotional biases in MDD with anxious distress compared with non-anxious MDD and HC participants. The specific aims and hypotheses of each chapter within this work are formulated as follows:

Chapter II presents a clinical trial (NeuroMood) that employed a single-blind randomised controlled trial design in MDD patients who insufficiently responded to standard treatments. The superiority of guilt-specific rtfMRI

neurofeedback was tested in the reduction of depressive symptoms and self-blame, while increasing self-esteem. Furthermore, it was investigated whether MDD patients in the rtfMRI neurofeedback group were able to decrease self-blame-selective hyper-connectivity between the rSATL and a posterior SC region (BA 25, see Figure I.1) and if improvements in symptoms in the neurofeedback group were associated with reduced self-blame-selective hyper-connectivity.

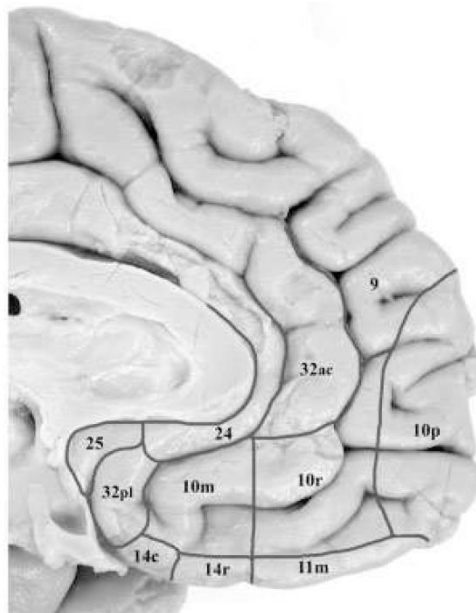


Figure I.1: Display of BA 25, the posterior subgenual target region in the NeuroMood study, which has previously been demonstrated to show hyper-connectivity with the rSATL as predictive of recurrence risk in remitted MDD (Lythe et al., 2015). BA 24 forms the anterior part of the subgenual cingulate cortex, which was found to show decreased connectivity with the rSATL in remitted DD with high self-contempt bias, irrespective of recurrence risk (unpublished secondary data analyses of Lythe et al., 2015). Figure adapted from Ongur, Ferry, & Price (2003).

The following hypotheses were postulated:

Hypothesis 1: Patients undergoing rtfMRI neurofeedback training will show reduced depressive symptoms, decreased self-blame and increased self-worth when compared with the psychological intervention group.

Hypothesis 2: Patients undergoing rtfMRI neurofeedback training will show decreased connectivity between the rSATL and the posterior SC post-treatment compared to pre-treatment.

Hypothesis 3: Decreased connectivity between the rSATL and the posterior SC region is associated with a reduction in depressive symptoms in MDD.

Chapter III of this thesis investigates differences in self-blaming emotional biases and clinical characteristics between MDD with and without anxious distress to better understand differences in their response to the psychological and rtfMRI neurofeedback intervention employed in the NeuroMood trial.

The following hypotheses were postulated:

Hypothesis 1: MDD patients with anxious distress show higher indignation/anger towards others as compared with MDD patients with non-anxious MDD.

Hypothesis 2: Self-blaming emotional biases will be more pronounced in MDD patients without anxious distress than MDD patients with anxious distress.

Hypothesis 3: MDD patients with anxious distress have experienced stressful life events more frequently than MDD patients without anxious distress.

Chapter IV presents the results of a novel experimental task, the social agency inference task (SAIT), specially developed for this thesis, and aimed at

elucidating the role of overgeneralised perceptions of preceding events in self-blaming emotional biases. This task thereby complemented previous tasks of self-blaming emotional biases, the modified version of the VMST as employed in previous chapters (II and III).

The following hypotheses were postulated:

Hypothesis 1: Patients with MDD show self-blaming emotional biases on the SAIT when compared with HC participants.

Hypothesis 2: Patients with MDD show an overgeneralisation of negative preceding actions internalising blame relative to those externalising blame when compared with HC participants.

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Chapter II: NeuroMooD trial

II.1) Abstract

Recent findings highlight the significance of excessive self-blaming emotions in major depressive disorder (MDD) and self-blame-selective hyperconnectivity between the right superior anterior temporal lobe (rSATL) and the posterior subgenual cortex (SC) is considered a potential biomarker of MDD recurrence risk. Real-time functional magnetic resonance imaging (rtfMRI) neurofeedback training was shown to be a feasible approach to modulating brain activity patterns in MDD. In this chapter, a single-blind randomised controlled trial is presented, designed to test the clinical benefits of a novel self-guided psychological intervention with and without additional rSATL-posterior SC rtfMRI neurofeedback, targeting self-blaming emotions in current and insufficiently remitted, early treatment-resistant MDD. Both interventions were demonstrated to be safe and therapeutically beneficial, resulting in a reduction of MDD symptom severity of 46% and response rates of more than 55%. Contrary to the hypothesis, no relationship was found between functional connectivity changes and changes in depressive symptoms. Differences in the clinical effectiveness of both interventions occurred between MDD patients with and without anxious distress. Although some contribution of placebo-like effects cannot be ruled out, the findings suggest that self-blame specific rtfMRI neurofeedback training may be superior over a solely psychological intervention in non-anxious MDD patients, which needs further confirmation in future studies.

II.2) Introduction

II.2.1) The need for developing novel interventions

Depression is found to be the leading cause of ill health, and disability worldwide (WHO, 2017, 2008) and can affect anyone at any point in life (Friedrich, 2017). One reason for this is found in the observation that individuals, who experience more than one major depressive episode (MDE), suffer an increased risk of facing further episodes in the course of the disorder (Eaton et al., 2008). The probability of further episodes rises to more than 70% after the second and more than 90% after the third MDE (American Psychiatric Association, 2000). A variety of pharmacological and psychotherapeutic treatment approaches have been established, aiming at reducing MDD symptoms; yet in most cases, even optimised, standard treatment approaches fail to prevent recurrence in most patients with MDD.

Meta-analyses show that pharmacological treatments (Viguera, Baldessarini, & Friedberg, 1998) and psychotherapy (Piet & Hougaard, 2011) are partially successful, reducing recurrence rates by 50% in the short-term; nevertheless, 60% of MDD patients experience further MDEs in the long run despite continuing medication (Viguera et al., 1998) or psychotherapy (Bockting et al., 2009). Further 30% of patients overall fail to achieve full remission, despite the provision of adequate treatment (Nierenberg & Amsterdam, 1990; Rush et al., 2006). In addition, there is no clear evidence that combining medication and psychotherapy improves long-term outcomes (Lampe, Coulston, & Berk, 2013) and a high proportion of patients are not amenable to either treatment option (Prins, Verhaak, van der Meer, Penninx, & Bensing, 2009). It is noteworthy that a

more recently published meta-analysis highlights the efficacy of mindfulness-based cognitive therapy (MBCT) as a powerful treatment in the prevention of recurrence within a 60 week follow-up period, irrespective of the number of MDEs patients have experienced in the past (Kuyken et al., 2016). Further, MBCT appears to be particularly beneficial for patients with pronounced residual symptoms (Kuyken et al., 2016). The authors remark, however, that the protective effects of MBCT in preventing recurrence in MDD diminish with time (Kuyken et al., 2016).

It can be concluded that there is an unmet need for developing novel treatment strategies aiming at effectively decreasing the patient's depressive symptoms and vulnerability for recurrence in MDD.

II.2.2) The neural basis of self-blaming emotional biases: a potential treatment target

Recent findings highlight the importance of excessive self-blaming emotions in MDD (Green, Lambon Ralph, Moll, Deakin, & Zahn, 2012; Green, Moll, Deakin, Hulleman, & Zahn, 2013). Using fMRI, abnormal functional connectivity between the rSATL and the anterior subgenual cingulate cortex was found to be associated with self-blame-specific emotional biases in remitted MDD (Green et al., 2012). The term 'functional connectivity' characterises a temporal interaction in fMRI data, describing the statistical association or correlation between anatomically distinct fMRI signal time courses, not implying how this correlation is mediated (Friston, 2011; Friston, Frith, Fletcher, Liddle, & Frackowiak, 1996).

It is noteworthy that increased functional connectivity within the rSATL –

posterior SC brain network was found to be predictive of elevated risk of future MDEs over the period of one year (Lythe et al., 2015), thereby identifying a potential fMRI biomarker of recurrence risk in MDD. These findings demonstrate that self-blaming emotional biases underlie the MDD patient's condition even in remitted stages of MDD and are in keeping with postulated cognitive and attributional theories of MDD, which emphasise the link between feelings of self-blame, the patient's negative self-concept (Beck, 1963), and overgeneralised self-blame and vulnerability for MDD (Abramson, Seligman, & Teasdale, 1978). Moreover, these results stress the profound impact of self-blame on MDD symptoms as well as its persistence in patients whose symptoms have subsided during periods of remission.

Whereas Moll et al. (2014) provided the technical proof-of-concept that changes in selective functional connectivity can be detected and fed back to healthy control (HC) participants during fMRI scanning, a recently completed double-blind, randomised clinical trial confirmed that fMRI neurofeedback can successfully train remitted MDD patients in rebalancing abnormal brain connectivity patterns (Zahn et al., 2018).

II.2.3) Real-time fMRI neurofeedback in major depressive disorder

Real-time fMRI neurofeedback is a training method that provides the individual with near real-time information about changes in neural activity to facilitate self-regulation of brain function, cognition and behaviour (Stoeckel et al., 2014; Thibault, Lifshitz, & Raz, 2016). It is a recent and less widely used experimental approach, yet using this technique, it has been demonstrated that individuals learn quickly to gain voluntary control over the activation and

connectivity of specific brain regions (Sulzer et al., 2013; Weiskopf, 2012). Only a few studies to this date have administered rtfMRI neurofeedback in patients with depression (Young et al., 2017a; Young et al., 2018a; Young et al., 2018b; Yuan et al., 2014; Zotev, Phillips, Yuan, Misaki, & Bodurka, 2014; Zotev et al., 2016), and even fewer studies investigated the use of rtfMRI neurofeedback as a therapeutic intervention strategy in MDD (Linden et al., 2012; Mehler et al., 2018; Young et al., 2017b; Young et al., 2014). Linden et al.'s (2012) pioneering study applied rtfMRI neurofeedback training targeted at increasing activation in brain areas involved in the processing of positive emotions, i.e. the ventrolateral prefrontal cortex and insula, whereas Young et al. (2014) used neurofeedback training to enhance amygdala response during the recall of positive autobiographical memories. Both studies assessed whether the rtfMRI neurofeedback interventions would have a significant effect on symptom severity in MDD as assessed with the 17-item Hamilton Rating Scale for Depression (Linden et al., 2012) and Profile of Mood States (POMS) depression ratings (Young et al., 2014). Although both studies delivered promising results and found significant reductions in symptom severity, it is noteworthy that they lacked randomisation and employed only small sample sizes (n=8 vs n=8 controls (Linden et al., 2012) and n=14 vs n=7 controls (Young et al., 2014)).

A more recently published study by Young et al. (2017a) was the first randomised rtfMRI neurofeedback trial in MDD, investigating medication-free individuals allocated to moderately sized groups (n=19 vs n=17 controls). Similarly to the authors' previous research approach (Young et al., 2014), rtfMRI neurofeedback was used in the aim of increasing the individual's amygdala hemodynamic response to positive autobiographical memories. Symptom

reduction was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS). Young et al. (2017a) observed a significant symptom reduction in patients allocated to the active neurofeedback group compared to a minimal response in the control neurofeedback group. Contrary to Young et al.'s results (2017a), another randomised controlled rtfMRI neurofeedback trial conducted by Mehler et al. (2018) did not find differences between the active and control rtfMRI neurofeedback MDD group. Interestingly, both rtfMRI neurofeedback groups successfully upregulated targeted brain areas and reduced their depression symptoms by more than 40%. Further, patients' symptoms remained stable at a follow-up assessment six weeks after trial completion (Mehler et al., 2018).

It is noteworthy that previous clinical rtfMRI neurofeedback studies focussed on investigating remission from depressed states rather than early treatment resistance or recurrence risk. Apart from recent work conducted by Mehler et al. (2018), to my knowledge, no rtfMRI neurofeedback intervention has been developed to this date which aims to reduce symptoms in MDD patients who have only insufficiently responded to standard treatment, a strong clinical predictor of recurrence risk in MDD. It has not been explored yet if the clinical benefits of rtfMRI neurofeedback as a therapeutic tool are more profound in those patients who only insufficiently respond to standard treatment, which is the reason why the NeuroMooD trial was conducted in early treatment-resistant MDD patients. Given the importance in finding that the self-blame-selective signature of hyper-connectivity between the rSATL and the posterior SC (Brodmann Area [BA] 25) is predictive of recurrence risk in MDD (Lythe et al., 2015), the

functional connectivity between those brain areas became target in the rtfMRI neurofeedback intervention in the NeuroMooD trial.

II.2.4) NeuroMooD trial: aims and objectives

Building on previous research findings as outlined above and grounded in the need for novel intervention strategies in the treatment of early treatment-resistant MDD, this research investigated and compared the effectiveness of two novel approaches.

Specifically, this clinical trial examined the clinical benefits of a novel rtfMRI neurofeedback protocol in current and insufficiently remitted MDD, aiming at self-blame-selective neural connectivity abnormalities between the rSATL and the posterior SC. The therapeutic effectiveness of this rtfMRI neurofeedback intervention was compared to the proposed benefits of a newly designed, self-guided psychological intervention. Clinically, both interventions aimed at alleviating symptoms of depression, and effectively reducing self-blaming emotions, in addition to ameliorating the sense of self-worth. Moreover, specific to the rtfMRI neurofeedback condition, the aim was to determine whether rtfMRI neurofeedback training might be effective in moderating both, excessive self-blame and depressive symptoms through the normalisation (i.e. decrease) of self-blame-related functional connectivity between the rSATL and the posterior SC (BA 25).

II.2.5) Hypotheses

The following hypotheses were postulated:

Hypothesis 1: Patients undergoing rtfMRI neurofeedback training will show reduced depressive symptoms, decreased self-blame and increased self-worth when compared with the psychological intervention group.

Hypothesis 2: Patients undergoing rtfMRI neurofeedback training will show decreased connectivity between the rSATL and the posterior SC post-treatment compared to pre-treatment.

Hypothesis 3: Decreased connectivity between the rSATL and the posterior SC region is associated with a reduction in depressive symptoms in MDD.

II.3) Methods

This clinical proof-of-concept trial received ethical approval from the NHS Health Research Authority, NRES Committee London – Camberwell St Giles (REC reference: 15/LO/0577) and was pre-registered on the ISRCTN registration database (identifier: ISRCTN10526888). Research funding was provided by King's College London and the Brain & Behavior Research Foundation. The single research site of this study constituted of the Institute of Psychiatry, Psychology & Neuroscience, King's College London.

Researchers involved in the conduction of this clinical trial affirm that study procedures complied with the ethical principles, standards and national and institutional guidelines for clinical trials and research involving human subjects and with the Helsinki Declaration of 1975, as revised in 2008.

II.3.1) Trial design

A single-blind, randomised controlled trial design was used, and participants allocated to two distinct treatment arms, each comprising three intervention visits (visits 2, 3 & 4). Regardless of the intervention group, treatment sessions were scheduled 7-13 days apart, depending on the participants' availability.

Feasibility and effectiveness of both interventional approaches were compared by measuring the change in clinical outcomes between pre-treatment (visit 1) and post-treatment assessments (visit 5).

One intervention condition implemented three sessions of a self-guided psychological intervention that consisted of cognitive reappraisal techniques,

modified from cognitive therapy (Beck, Rush, Shaw & Emery, 1979) and related approaches. Assigned to the second intervention condition, the rtfMRI treatment group, participants were asked to apply the same self-guided psychological strategies during three sessions of rtfMRI neurofeedback training, targeting rSATL-posterior SC correlation.

It is important to mention that initially the NeuroMooD study was designed to compare three treatment arms, investigating the treatment effects of rtfMRI neurofeedback with an active, cathodal and a sham transcranial direct current stimulation (tDCS) intervention. Specifically, the original single-blind, randomised controlled design compared three sessions of the rtfMRI neurofeedback treatment as described above with three sessions of right superior temporal lobe cathodal tDCS plus self-guided psychological intervention and three sessions of sham right superior temporal lobe tDCS plus self-guided psychological intervention. Due to funding reasons, the original trial design had to be modified, and the data of 6 randomised participants, that had already been collected, was discarded.

II.3.2) Randomisation method

The randomisation of trial participants was performed by an automatised online system, set up by the Clinical Trials Unit, King's College London. The randomisation process implied a stratified block design with randomly varying block sizes, deploying two stratification factors: gender (female/male) and baseline scores of the primary outcome measure, the Beck Depression Inventory-II (BDI-II; Beck, Steer & Brown, 1996). Baseline scores classified participants

based on designated BDI-II categories of symptom severity as follows: BDI-II scores below 14 points indicating minimal depression, BDI-II scores between 14 and 28 points comprising mild and moderate depression and BDI-II scores of 28 points or higher, implying severe depressive symptoms. Participants were informed about their allocated treatment group upon completion of the baseline clinical and neuropsychological testing on their pre-treatment assessment (visit 1).

II.3.3) Recruitment and reimbursement of participants

The recruitment/randomisation phase consisted of a total of 15 months, from September 2016 to December 2017. Trial adverts were posted primarily online, further recruitment strategies entailed the dissemination of study adverts via university and institutional recruitment circulars, as well as presenting to self-help groups at scheduled member meetings.

Participants received compensation for the time taken to participate in the study in the form of high street gift vouchers or shopping vouchers. Reimbursement was appointed on a pro-rata basis on the final day of participation: vouchers worth £10 for the pre-trial assessment session (visit 1), vouchers worth £20 per treatment session ($3 \times £20 = £60$ for visit 2, visit 3 and visit 4). Additional vouchers worth £30 for the final follow-up session (visit 5).

II.3.4) Inclusion criteria

Recruitment for this clinical trial was targeted at patients suffering from recurrent MDD according to diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA], 2013), with a minimum of one past MDE of at least a two months duration. At

baseline assessment (visit 1), patients either currently experienced an MDE or, insufficiently remitted, presented with significantly impairing or bothering symptoms, despite not fulfilling MDE criteria anymore. It was required that remaining symptoms would be significant in severity, classified as a psychiatric status rating of three (i.e. significant symptoms) or four (i.e. major symptoms) on the Longitudinal Interval Follow-up Interview (LIFE; Keller et al., 1987) over the past two weeks prior baseline assessment and randomisation. Further, MDD patients needed to be stable in symptoms for at least six weeks before randomisation to minimise the risk of including spontaneous remitters.

Importantly, MDD patients were required to have shown an only insufficient response to at least one psychological intervention (e.g. cognitive behavioural therapy) or antidepressant medication before their enrolment in the study or were found to be not amenable to standard forms of intervention. MDD patients could only be included if they were not currently undergoing psychotherapeutic treatment.

Antidepressant medication was no exclusion criterion, but patients needed to be on a stable dose for at least six weeks without improvement before their participation and were asked to remain on this stable dose throughout the study.

Lastly, participants needed to be aged 18 years or older, right-handed (to ensure homogenous responses to the right hemispheric treatment target), and be proficient in English, so that reliable responses on newly developed secondary outcome measures could be collected.

II.3.5) Exclusion criteria

To ensure safety and minimise potential health risks, participants needed to be excluded if they presented with greater than a low risk of suicidality, violence or current self-harming behaviour. Additionally, participants presenting with a current MDE of lasting more than 12 months were excluded to not inhibit patients from accessing standard forms of treatment.

Additional exclusion criteria were defined as follows:

- i. Standard MRI contraindications, i.e. non-removable ferromagnetic devices or implants due to the possible dangerous effects of the MRI magnet upon metal objects in the body
- ii. History of manic or hypomanic episodes, of schizophreniform symptoms or schizophrenia, or substance abuse
- iii. History of neurological disorders such as seizures, loss of consciousness following brain injury or medical disorders affecting brain function, blood flow or metabolism
- iv. History of learning disabilities, major medical, developmental or relevant other axis-I disorders
- v. Prior specialist diagnosis of attention deficit hyperactivity disorder (ADHD), antisocial or borderline personality disorder
- vi. Significant impairment of psychosocial functioning before the last MDE indicating the possibility of a comorbid personality disorder
- vii. Current intake of benzodiazepines, GABAergic or benzodiazepine receptor agonists
- viii. Current recreational drug use
- ix. Past violence or current aggressive impulses

- x. Impairments of vision or hearing which cannot be corrected during the treatment sessions
- xi. Pregnancy

II.3.6) Assessment and evaluation of participants: eligibility assessment

The participant selection process commenced with a telephone-based screening of volunteers for inclusion and exclusion criteria. Before starting the formal evaluation, volunteers were informed about the content and rationale of the screening, and oral consent was obtained. In instances where volunteers met inclusion criteria following the phone screening interview, volunteers were invited to attend the pre-trial assessment (visit 1) to confirm their trial eligibility. Volunteers received a formal invitation via email asking candidates to read through the attached participant information sheet and study consent form. Importance was placed on ensuring that volunteers received both, information sheet and consent form, at least 24 hours before their initial study visit to allow for enough time to familiarise themselves with details about the trial and the conditions of their participation. Find the phone screening template attached as Appendix A.

During the recruitment phase, a total of 311 volunteers interested in participating in the study were screened over the phone, and 71 volunteers attended the initial baseline assessment (visit 1). Following diagnostic and clinical evaluation, ultimately, N=43 participants were randomised into the study, of which n=35 participants completed this clinical trial.

II.3.7) Assessment and evaluation of participants: clinical assessment

The diagnostic, clinical and cognitive assessment comprised standardised, validated measures that have been used extensively in psychiatric research.

Summary of standard clinical and cognitive instruments:

- i. Structured Clinical Interview (SCID) for DSM-5 (First, 2015)
- ii. AMDP Psychopathology Interview questions on depression (Faehndrich & Stieglitz, 1997)
- iii. Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987)
- iv. Clinical Global Impression (CGI-) Scale (Busner & Targum, 2007)
- v. Beck Depressive Inventory (BDI-II; Beck et al., 1996)
- vi. Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979)
- vii. Quick Inventory of Depressive Symptomatology (QUIDS-SR16; Rush et al., 2003)
- viii. Hypomania Checklist-16 (Forty et al., 2010)
- ix. Rosenberg Self-Esteem Scale (Rosenberg, 1965)
- x. Profile of Mood States (POMS) Scale (McNair, Lorr & Dropplemen, 1971)
- xi. MINI International Neuropsychiatric Interview (module on suicidality only; Sheehan et al., 1998)
- xii. Psychiatric Family History Screen (Weissman et al., 2000)
- xiii. Life Events Questionnaire (Brugha & Conroy, 1985)
- xiv. Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998)
- xv. Altman Self-Rating Mania Scale (Altman, Hedeker, Peterson & Davis, 1997)

- xvi. Addenbrooke's Cognitive Examination (ACE-III; Hsieh, Schubert, Hoon, Mioshi & Hodges, 2013) in patients >50 years only

In addition to the abovementioned scales and measures, clinical evaluation of participants further entailed a non-structured clinical interview, as well as the documentation of the patient's medical history and in females the day in their menstrual cycle. Furthermore, age at onset, episode duration(s), and total illness duration was recorded, along with details about the course of illness, i.e. number of episodes and medication history.

II.3.8) Additional experimental neuropsychological testing

Supplementary to clinical and cognitive assessments, participants were asked to provide ratings of autobiographical memories associated with feelings of self-blame and other-blame. Moreover, additional experimental tasks developed by our research group were administered, designed to explore neurocognitive aspects of implicit self-contempt biases and self- and other-blaming emotions:

- i. A modified short version of the VMST (Zahn et al., 2015a): this computerised task investigates emotions related to self-blame (i.e. guilt, shame, self-contempt, self-disgust, self-directed anger) versus blaming others (indignation, anger, contempt or disgust towards others). Preceded by the description of hypothetical scenarios of social behaviours of the participants themselves and their best friends, participants are instructed to select the emotion they are most likely to experience. We added items related to action tendencies (Roseman, Wiest & Swartz, 1994), previously validated in an unpublished study. The following action tendencies were

measured: creating distance from self, hiding, apologising, creating distance from friend, verbally or physically attacking/punishing friend or no action/other action. This task is presented in more detail in chapter III.

- ii. A modified version of the social knowledge differentiation task (Green et al., 2013): this computerised, neuropsychological test examines the participant's ability to access differentiated social conceptual knowledge when instructed to appraise hypothetical scenarios of social behaviour of different contexts of agency (self-agency vs other-agency). The task was modified by restricting the original task to 30 items, focussing on negatively valenced scenarios only.
- iii. Brief Implicit Association Test (BIAT): this computerised task was developed by our research group in collaboration with Prof Rüsch and Dr Bogenhausen. It is an indirect measure of self-contempt bias, evaluating the association of contempt or disgust with oneself relative to others. The task design is based on similar tests that have been validated to measure implicit self-esteem (Greenwald & Farnham, 2000). This task is presented in more detail in chapter III.
- iv. Social agency inference task (SAIT): Specifically developed for this research project, this computerised task assesses whether changes in the perception of social agency underpin self-blaming biases in MDD. Chapter IV explains in detail how this task was constructed.

Clinical and cognitive assessments, along with the administration of additional experimental neuropsychological tests were carried out by me, with exception of the AMDP, the Global Assessment Functioning (GAF) Scale, the

Social and Occupational Functioning Assessment Scale (SOFAS) and observer-rated outcome measures. For particulars on the assessor of outcome measures refer to section II.3.10. To optimise the quality of all assessments performed, I have received extensive clinical and diagnostic training, provided by a consultant psychiatrist, before the conduction of this study.

An overview of research design and temporal staging of assessments throughout the study is depicted in the trial schedule presented in section II.3.9 of this chapter.

II.3.9) Trial schedule chart

	Initial Patient Contact	Pre-Trial Assessment Visit 1	Treatment Session Visit 2	Treatment Session Visit 3	Treatment Session Visit 4	Post-Trial Assessment Visit 5
	[email & phone]	[day 0]	[1-13 days after visit 1]	[7-13 days after visit 2]	[7-13 days after visit 3]	[7-13 days after visit 4]
Oral informed consent	✓					
Introduction to the clinical trial	✓					
Assessment of eligibility	✓	✓				
Written informed consent		✓	✓	✓	✓	✓
Clinical & neuro-psychological assessment		✓				✓
Psychological Intervention only			✓	✓	✓	
rtfMRI neurofeedback training			✓	✓	✓	
Mood assessment		✓	✓	✓	✓	✓
Risk assessment		✓	✓	✓	✓	✓

II.3.10) Pre-registered outcome measures

Outcome measures comprised self-rated and observer-rated scales and assessments along with fMRI connectivity analyses as specified below. Observer-rated outcomes were assessed by a senior psychiatrist (R.Z.) who was blinded to the treatment group allocation of participants throughout the trial.

Primary outcome measure

The primary outcome measure was defined as the reduction of depressive symptoms between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with the BDI-II.

Secondary outcome measures

In addition to the primary outcome measure, the following secondary outcome measures had been pre-registered before the begin of the trial:

- i. Reduction of depressive symptoms between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with MADRS
- ii. Reduction of self-rated depressive symptoms between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with QUIDS-SR16
- iii. Reduction of self-rated depressive symptoms between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with POMS depression-dejection subscale

- iv. Increase in self-worth between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with Rosenberg Self-Esteem Scale
- v. In the rtfMRI neurofeedback group: decrease in post vs pre-training rSATL–posterior SC correlation for self-blame relative to blaming others between the first and last treatment session (i.e. at the start of visit 2 and at the end of visit 4), using fMRI as measured by regression coefficients for the time series, as extracted by the software FRIEND (Functional Real-time Interactive Endogeneous Neuromodulation and Decoding; Basilio et al., 2015; Sato et al., 2013)
- vi. Reduction in implicit self-blaming bias between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with BIAT (subcategories contempt–anger and contempt–anxiety)
- vii. Reduction in agency-incongruent self-blame between pre-treatment visit 1 and post-treatment visit 5 (7-13 days after final treatment session) as assessed with the short version of the VMST
- viii. Self- and observer-rated clinical global impression at post-treatment visit 5 (7-13 days after final treatment session) as assessed with the CGI-Scale
- ix. Withdrawal rates throughout the trial and separately for the period after the first treatment session until post-treatment visit 5 (7-13 days after final treatment session)
- x. Adverse events throughout the trial and separately for the period after the first treatment session until post-treatment visit 5 (7-13 days after final treatment session)

- xi. Reduction in self-rated self-blame as assessed with the mean of self-blame ratings of two guilt-specific autobiographical events obtained prior the first (visit 2) and after final treatment session (visit 4)
- xii. Reduction in observer-rated self-blame as assessed with the Moral Emotion Addendum to the AMDP as the sum of all self-blaming emotion scores at baseline (visit 1) and post-treatment at visit 5 (7-13 days after final treatment session)

II.3.11) Intervention procedures

Both interventions, the psychological intervention as well as the rtfMRI neurofeedback training, consisted of three individual treatment sessions, scheduled 7-13 days apart, and involved equivalent preparation processes prior to the first treatment session.

Before the first interventional session, participants were asked to provide two cue words, prompting them to remember two autobiographical events that would cause them to experience strong feelings of self-blame and guilt. Also, participants provided two cue words reminding them of life events where they experienced substantial feelings of indignation or anger towards other people while feeling low levels of self-blame.

Before and after each treatment session, participants rated the intensity of evoked self-blame and indignation feelings on a Likert-type scale from 0 to 10. Moreover, they rated (from 0 to 10) how successful they felt in the emotional training during the intervention and estimated the percentage of time (0-100%) that they were able to focus during the session.

Concluding each treatment session, the participant's suicidality risk was assessed using the MINI International Neuropsychiatric Interview suicidality module, focussed on the time period since the previous study appointment. In addition, the severity of depressive symptoms was monitored and assessed with the BDI-II. Participants were excluded if they expressed a suicidality risk greater than low, or if their depressive symptoms had worsened, as reflected in an increase of 10 points or more on the BDI-II compared to the baseline score prior randomisation. In such an instance, the protocol requested to un-blind the leading senior psychiatrist of the NeuroMooD trial (R.Z.), who discussed treatment recommendations with the patient if requested. By doing so, participants were assisted in accessing standard treatment options swiftly.

II.3.12) Psychological intervention

In the psychological intervention group, the cue words provided by participants of this treatment arm were programmed into a timed presentation format and played back to them during each treatment session. To help participants manage their feelings of self-blame constructively, they were instructed to use specific, self-guided psychological strategies. Participants were suggested to use the following strategies to help them manage their feelings, yet they could also develop their own strategies:

- i. Think about why you might not have been in control over the outcome of the event.
- ii. Think about why you might not be responsible for the outcome of the event.
- iii. Think about why the consequences for others might not be so bad.
- iv. Think about making up for things or apologising.

- v. Think about the other person forgiving you.
- vi. Think about forgiving yourself.

These strategies were based on (1) attribution theory which highlights the importance of locus of control for self-blame (Abramson et al., 1978), on (2) omnipotent responsibility associated with depressogenic forms of guilt (O'Connor, Berry, Weiss, & Gilbert, 2002), on (3) neurocognitive models of self-blame, implicating representations of future consequences as important to guilt-proneness (Zahn R, de Oliveira-Souza & Moll, 2013), on (4) the associations of reparative action tendencies with adaptive forms of guilt (Tangney, Stuewig, & Mashek, 2007), as well as on (5) the focus on forgiveness and self-kindness as thematised in compassion-focused therapy (CFT; Gilbert, 2009a, 2009b; Gilbert & Procter, 2006).

The intervention consisted of four parts. In the first and the fourth part, participants were asked to only think about the autobiographical events triggered by their cue words, without using any strategies to manage their feelings of self-blame. Before the second and third part of the intervention, participants were instructed to start using one or more self-guided strategies when seeing their guilt cue words to manage their feelings of self-blame constructively.

Participants were given the following instructions before the treatment session was started:

'At the beginning and end of the session, you will have to think about the self-blame and anger events when shown your cue words. In between, you will be asked to keep thinking about the self-blame event while trying to use one or more strategies that best help you to cope with the self-blaming feeling. When

numbers are presented on the screen, you will have to subtract seven from the number displayed.’

In the first and fourth part of the presentation, participants were shown their guilt, and their indignation cue words, parts two and three only contained the patient’s guilt cue words and no indignation provoking cue words. Parts 1 and 4 were 408 seconds in length, including emotional blocks (guilt and indignation) and subtraction blocks, plus a 30-second reminder of task instructions. Parts 2 and 3 consisted of a time sequence of 424 seconds each, containing guilt cue words and subtraction blocks, in addition to the display of instruction slides for 60 seconds. Consequently, the intervention part of each treatment session was completed after approximately 30 minutes.

The order of the displayed cue words and numbers was as follows:

Part 1 of the intervention: instruction to only think about the autobiographical events without using psychological strategies → number → guilt cue word 1 → number → indignation cue word 1 → number → guilt cue word 1 → number → indignation cue word 1 → number → guilt cue word 2 → number → indignation cue word 2 → number → guilt cue word 2 → number → indignation cue word 2

Part 2 of the intervention: instruction to keep thinking about the events, while trying to use psychological strategies to cope with self-blaming feeling → number → guilt cue word 1 → number → guilt cue word 1 → number → guilt cue word 2 → number → guilt cue word 2

Part 3 was equal to part 2 of the intervention: instruction to keep thinking about the events, while trying to use psychological strategies to cope with self-blaming feelings → number → guilt cue word 1 → number → guilt cue word 1 → number → guilt cue word 2 → number → guilt cue word 2

Part 4 of the intervention: instruction to only think about the autobiographical events without using psychological strategies → number → indignation cue word 1 → number → guilt cue word 1 → number → indignation cue word 1 → number → guilt cue word 1 → number → indignation cue word 2 → number → guilt cue word 2 → number → indignation cue word 2 → number → guilt cue word 2.

The mental subtraction blocks served as a distraction from the emotional load of the participants' thought processes and to separate each emotional block. Self-blame cue words were presented in blue colour on a black background; indignation cue words appeared in red on black background and numbers were presented in yellow.

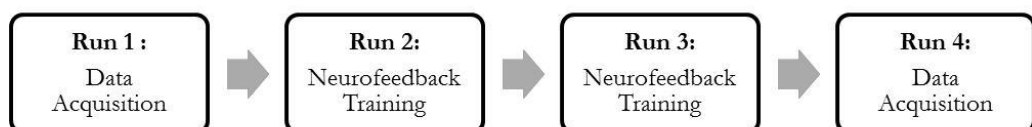
In both treatment groups, participants were instructed to implement the psychological strategies in their everyday lives and to use them in-between treatment visits whenever feelings of self-blame would arise. The frequency of use was recorded at the next treatment visit. Participants were instructed to continue using the strategies until the final assessment visit (visit 5).

II.3.13) Real-time fMRI neurofeedback intervention

The rtfMRI neurofeedback intervention aimed at targeting hyper-connected brain correlation patterns between the rSATL seed and the posterior SC region of interest (ROI). In remitted MDD, functional hyper-connectivity between these brain areas was postulated to portray the neural signature of overgeneralised self-blaming emotions in depression, as remitted MDD patients were found to display abnormally increased connectivity when experiencing self-blaming emotions relative to experiencing other-blaming emotions such as indignation (Lythe et al., 2015).

Analogous to the psychological intervention group, and before the first neurofeedback training session, participants were asked to decide on specific autobiographical memories that would evoke strong feelings of self-blame and other-blame when prompted by previously defined cue words. The self-blame-evoking scenarios had to involve the participant as the main agent of the scenario. The other-blaming scenarios had to involve another person acting. To evaluate whether a change occurred in the attribution of blame, ratings on these events were obtained before and after each scanning session. Instructions were given through the MRI intercom, participants, however, responded with a button box to prevent extensive head movement while being in the scanner.

Analogue to the psychological intervention group, each of the three rtfMRI neurofeedback sessions contained a paradigm of four runs, whereby the following procedure applied:



The first and fourth run (204 volumes each; 408 seconds duration) were identical and served to determine pre- and post-neurofeedback effects. They constituted of rtfMRI data acquisition runs, consisting of four self-blame (guilt) blocks (15 volumes each) and four other-blame (indignation) blocks (15 volumes each), interspersed with eight mental subtraction condition blocks (10 volumes each). As mentioned earlier, during the subtraction blocks, participants were asked to mentally subtract seven from a 3-digit number (e.g. 101, 102).

While run 1 measured the correlation coefficient of self-blaming emotions relative to other-blaming emotions (indignation), training effects on such correlations were assessed in run 4.

During the neurofeedback training runs (run 2 and 3), an upward and downward moving thermometer scale was displayed to provide visual feedback on how successful participants were in modifying their brain correlation patterns between the rSATL seed and the posterior SC region ROI. The thermometer scale appeared in the form of a bar filled with colours that could reach different levels. Participants were instructed to think about the particular autobiographical scenario triggered by the display of the previously agreed cue word and to try and bring up the level to the top of the thermometer scale by using the psychological strategies they had been equipped with before the scanning session.

Runs 2 and 3 (212 volumes each; 424 seconds duration) were identical and consisted of four guilt blocks (42 volumes per block), interspersed with four mental subtraction condition blocks (10 volumes each).

Similar to the psychological intervention group, mental subtraction blocks were used to divert participants from the emotionally charged autobiographical memories, in addition to minimising resting-state activity in the posterior SC

region (Bado et al., 2014).

II.3.14) Real-time fMRI neurofeedback method

The rtfMRI neurofeedback software FRIEND (Basilio et al., 2015; Sato et al., 2013) was used in the file version 1.0.0.257. It is noteworthy that FRIEND has previously been validated for correlation feedback in patients with MDD (Zahn et al., 2018).

A detailed description of methodological specifications of FRIEND as a rtfMRI neurofeedback tool is provided by Sato et al. (2013) and Zahn et al. (2018). In the NeuroMooD trial, FRIEND provided ROI-based rtfMRI neurofeedback alongside executing fundamental pre-processing steps of fMRI data in real-time. Facilitated by native FSL codes, FRIEND performed motion correction using MCFLIRT, spatial smoothing with Gaussian Kernel (FWHM = 6mm) and GLM calculation (Zahn et al., 2018).

Signal-level normalisation was performed by subtracting the mean value of the voxels signals within the ROI over the entire preceding subtraction condition block from the current echo-planar images belonging to the guilt or indignation condition block, which minimises local signal trends (Zahn et al., 2018).

The rSATL seed and posterior SC ROI were pre-defined, warped from MNI space into subject space and ultimately back-transformed into native space, using inverse transformation algorithms of FSL FLIRT (affine, 12 parameters) (Zahn et al., 2018). During run 1, 50% of the most activated voxels were selected in the native space ROI, contrasting the activation between guilt vs subtraction in the rSATL ROI, while contrasting guilt vs indignation in the posterior SC ROI.

These voxels were used to extract the average signal for the subsequent rtfMRI neurofeedback training. The first five volumes of each emotional block were discarded due to high correlations guided by a decrease in time series after subtraction conditions (Zahn et al., 2018).

Thermometer levels, as displayed in the neurofeedback training runs, were calculated from the participant's correlation patterns with a delay of six seconds. Once the first ten time points had been acquired to compute a correlation coefficient, the thermometer was updated every two seconds as soon as a new time point had been collected (i.e. each acquired volume).

FRIEND used a moving target correlation algorithm over a sliding time window of the last ten volumes, updated every two seconds, hence for each acquired volume. The minimum of the thermometer display was calculated based on the minimum value of the last 10 Pearson correlation coefficients, whereas the maximum of the thermometer was calculated based on the maximum value of the last ten correlations.

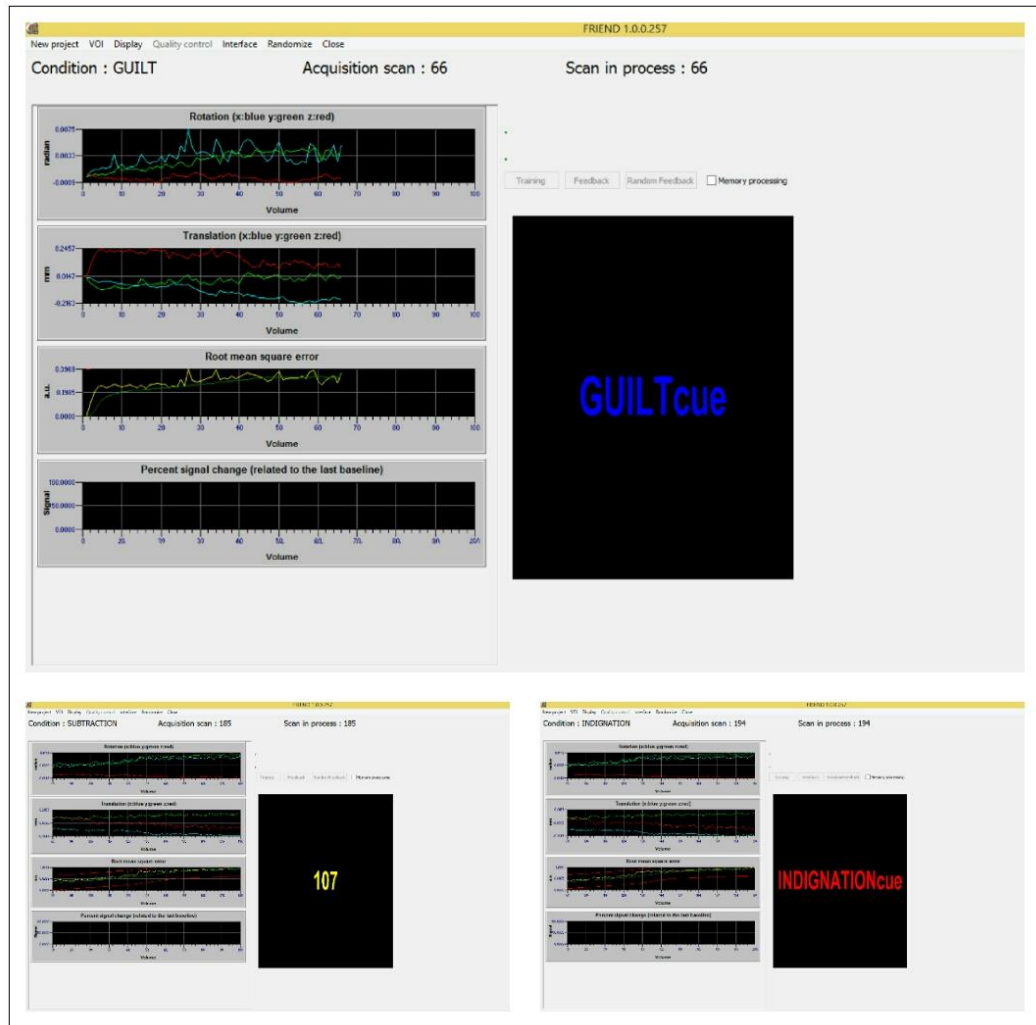


Figure II.1: Display of the interface of the rtfMRI neurofeedback software FRIEND during a data acquisition run. During acquisition runs (run 1 and 4), participants are presented with their guilt and indignation cue words. Cue words refer to autobiographical memories of events that trigger patients to experience feelings of self-blame or indignation. During these runs, participants are solely thinking about these events and are not using any psychological strategies to manage associated feelings of guilt. In-between the emotional conditions, participants are presented with numbers which cue them to perform mental subtractions from a number displayed at the screen.

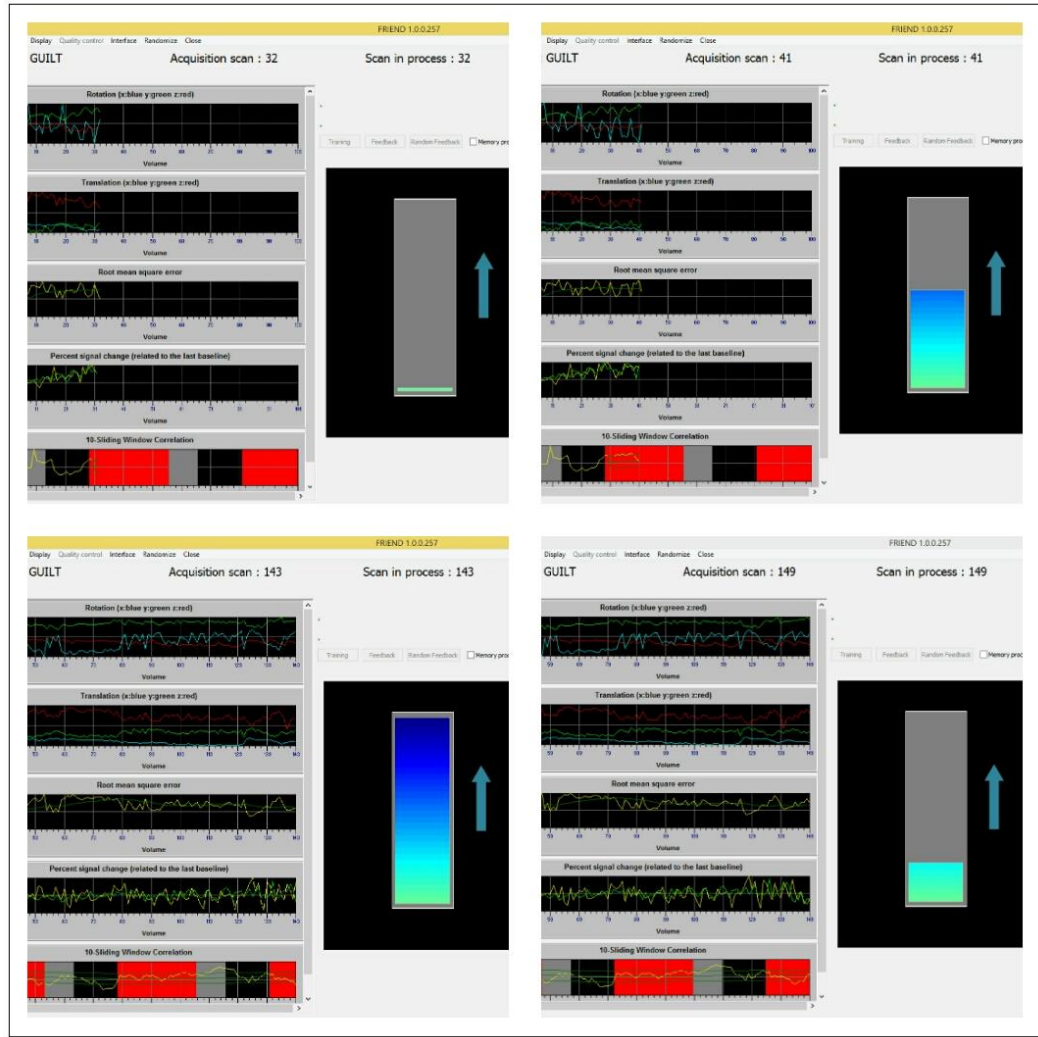


Figure II.2: Display of the interface of the rtfMRI neurofeedback software FRIEND during a neurofeedback training run. In the scanner, participants are presented with their individualised guilt cue words or subtraction blocks. In the guilt condition, a thermometer display containing a moving colour bar appears and represents visual feedback of the patient's functional connectivity patterns in real-time. During the rtMRI neurofeedback runs (run 2 and 3), participants are asked to bring up the level of the thermometer by using psychological strategies when thinking about autobiographical, guilt evoking events. The colour bar rises if functional (hyper-)connectivity between the rSATL and posterior SC successfully decreases.

II.3.15) Image acquisition

MRI scan facilities were booked at the Centre for Neuroimaging Sciences, King's College London. Image acquisition was carried out on an MR750 3.0T MR system (General Electric), using a hyperbolic secant (HS) excitation pulse, optimised for orbitofrontal and inferior temporal regions, minimising signal dropout (Wastling & Barker, 2015). A 32-channel head coil was chosen to support an optimal signal-to-noise ratio.

Functional image acquisition was obtained in the AC-PC plane, top to bottom, using a T2*-weighted echo-planar imaging EPI (BOLD) sequence (TR = 2000 ms, TE = 30 ms, matrix = 64x64, FOV = 211 mm, flip angle = 73°, voxel size = 3x3x3 mm; slice thickness = 3 mm, slice gap = 0.3 mm, 36 slices). Auto shimming was applied before starting each experimental run, acquiring four additional volumes which were automatically discarded, accounting of T1 equilibration effects.

High-resolution anatomical images were acquired with a magnetisation-prepared rapid gradient echo (MP-RAGE) sequence (TR = 7.3 sec, TE = 3.0 sec, matrix = 256 x 256, FOV = 270 mm, slice thickness = 1.2 mm, 196 slices).

Clinical images were acquired on the first day of treatment (visit 2) using an FRFSE (2 mm thickness, 72 slices) and FLAIR sequence (4 mm thickness, 36 slices) and checked for anatomical brain abnormalities after the treatment session by a radiologist at the Centre for Neuroimaging Sciences, King's College London, independent of additional, internal checks completed by the NeuroMooD study team.

While being in the MRI scanner, the participant's head motion was restricted using padding and heart rate measurements recorded via a finger pulse

sensor. A mirror fitted to the head coil allowed MDD patients to view visual stimuli presented during image acquisition, i.e. autobiographical cue words and the visual feedback thermometer, as stimuli were projected to a screen located behind the participant's head. Verbal instructions were communicated via the MRI intercom, participants, however, were instructed to respond using a button box placed in their hands to avoid incidental head movement.

II.3.16) Statistical power and offline analyses

Statistical power was calculated using G*POWER software and required a sample size of $n=34$ participants to achieve 85% power at $p=.05$, 2-sided (t-test). This calculation was based on a conservatively estimated effect size ($d=1.06$) lower than the effect size ($d=1.5$) reported in a previous rtfMRI neurofeedback study in MDD (Linden et al., 2012). The enrolment target consisted of $n=45$ MDD patients, including a 20% drop-out rate of 9 participants. Hence, this trial aimed to conclude with $n=36$ MDD study completers, above $n=34$ as needed per power calculation.

Given that this clinical trial was conducted as a pilot study to test feasibility, the performed power calculation is not recommended as it is based on effect sizes which may have been inflated due to small sample sizes. To determine precise effect sizes, pilot studies are recommended to include at least 70 participants (i.e. 35 participants per group) when estimating the pooled standard deviation for continuous outcomes in randomised controlled trials (Teare et al., 2014). Furthermore, based on guidelines posited by the National Institute for Health Research, feasibility studies should not intend to be based on standard power calculations (Teare et al., 2014).

Ultimately, $n=43$ participants were randomised into the study, whereby $n=22$ MDD patients were allocated to the fMRI neurofeedback group and $n=21$ to the psychological intervention group. A sum of 8 participants withdrew or was excluded during the duration of the trial, leading to a final of $n=35$ datasets for the analysis of the primary outcome measure (BDI-II). Further details about participant numbers and withdrawal rates in both treatment groups can be found in section II.3.6 and section II.4.3 and are included in the trial flow diagram in section II.3.17.

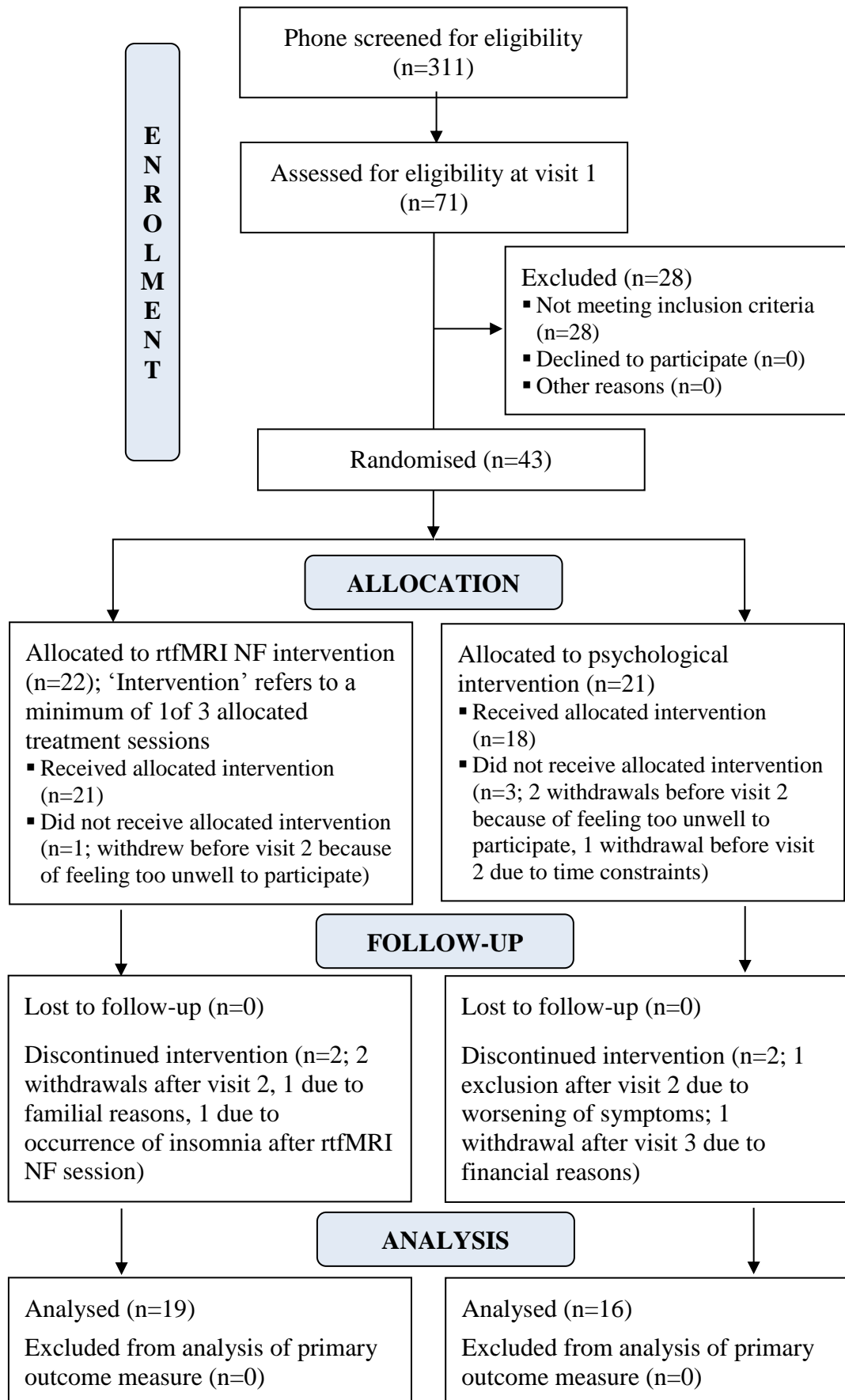
Statistical analyses were executed using the software package IBM SPSS Statistics 24 (<https://www.ibm.com/analytics/spss-statistics-software>). Group-level analyses of primary and secondary outcomes, comparing pre- and post-treatment effects (visit 1 vs visit 5), were obtained using the constrained longitudinal analysis (cLDA) model, the alpha-level was set to $p=.05$, two-tailed. Cohen's d effect sizes were computed using the formula: $2 \times t\text{-value} / \text{square root of degrees of freedom (df)}$ (Rosenthal & Rosnow, 1991). Where cLDA was inapplicable, intervention group comparisons were performed using Mann-Whitney U tests and generalised linear models (ordinal logistics).

A repeated measures ANOVA was chosen in the analysis of regression coefficients for z-transformed rSATL and posterior SC signals in the guilt and indignation conditions. Transforming the data into z-transformed values allowed for receiving standardised regression coefficients.

Explorative data analyses of the anxious distress subtype of MDD were conducted using univariate GLM analysis, for secondary correlation analyses investigating functional connectivity changes, self-esteem and engagement in

treatment, Spearman's rho was computed. As analyses were either hypothesis-driven or exploratory (secondary outcome measures in the feasibility trial), p-value adjustments to correct for multiple comparisons were not carried out (Feise, 2002).

II.3.17) Trial flow diagram



II.3.18) NeuroMooD protocol violations

Minor violations of the NeuroMooD protocol occurred during the duration of this study due to difficulties in scheduling participants' treatment and final assessment visits. Modified schedules had to be arranged for individual participants who were unable to attend study visits within the preferred interval of 7 to 13 days between appointments due to time constraints. Also, limited availability of fMRI scanning slots at the MRI facilities of the Centre for Neuroimaging Sciences, King's College London, affected MDD patients allocated to the rtfMRI neurofeedback group, occasionally causing a delay in the scheduling of treatment visits. As this issue became apparent early in the study, treatment visits for the psychological treatment group were scheduled in intervals comparable to those of the rtfMRI neurofeedback group. Ultimately, no significant difference was found between treatment groups regarding the total number of days included in the study ($t=1.21$, $df=33$, $p=.237$, two-tailed), considering the period from randomisation (visit 1) until trial completion (visit 5). On average, it took rtfMRI neurofeedback participants 40 days ($SD=9.18$) to complete the NeuroMooD trial. Similarly, participants randomised to the psychological intervention group participated on average for 37 days ($SD=7.37$).

II.4) Results

II.4.1) Clinical characteristics of participants

Table II.1: Clinical characteristics of intervention groups

	PSYCHOLOGICAL (n=16)	NEUROFEEDBACK (n=19)
Number of previous MDEs (percentiles)	25 th =2 50 th =4.5, 75 th =13.75 range: 2-66	25 th =3 50 th =4, 75 th =8 range: 1-110
Current MDE	9	10
Partially remitted	7	9
MDD DSM-5 subtype		
Anxious Distress	4	11
Melancholic Features	1	2
Melancholic Features + Anxious Distress	3	2
Atypical Features	0	1
Atypical Features + Anxious Distress	1	0
None	7	3
Current medication		
Psychotropic medication	10	10
Antidepressant (therapeutic dose)	9	9
Of which SSRI	6	6
Life-time co-morbidity		
Current Persistent Depressive Disorder of the dysthymic subtype	2	3
Past PTSD with residual symptoms	2	3
Past PTSD fully remitted	0	1
Current Social Anxiety Disorder	1	2
Past Social Anxiety Disorder	0	2
Past Anorexia Nervosa	0	1

Participants in the psychological intervention and rtfMRI neurofeedback groups did not differ on median numbers of previous episodes despite higher percentiles in the psychological intervention group ($U=145$, $p=.832$, two-tailed). MDE = major depressive episode, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, PTSD = posttraumatic stress disorder; m = male, f = female; M = mean, SD = standard deviation, [M-M] = Minimum-Maximum. In the rtfMRI neurofeedback group, one participant was suspected of displaying symptoms of autism spectrum disorder; one participant showed symptoms

of attention deficit hyperactivity disorder during childhood, one participant reported past heavy alcohol and substance use.

Table II.2: Demographic characteristics of intervention groups

	PSYCHOLOGICAL	NEUROFEEDBACK
Sex	4m/12f	3m/16f
	M;SD;[Min-Max]	M;SD;[Min-Max]
Age in years	37.63;9.74;[22-55]	36.74;11.04;[20-59]
Years of education	18.06;2.52;[13-22]	16.95;3.15;[11-23]

Participants of both treatment groups did not differ in age ($t=-2.50$, $df=33$, $p=.804$) or years of education ($t=-1.14$, $df=33$, $p=.262$).

II.4.2) Pre-registered outcome measures: primary outcome measure

A significant improvement, irrespective of treatment group, was found on the pre-registered primary outcome measure, the BDI-II (Beck et al., 1996). A comparison of BDI-II score means pre- and post-treatment showed an overall reduction of 46.07%, which corresponds to a baseline assessment ($N=43$) of $M=29.14$ points ($SD=8.66$) and $M=15.71$, ($SD=9.75$) on the final assessment day ($n=35$). CLDA estimated the effect of time as a post-treatment BDI-II score mean of $M=13.39$, $SE=2.74$, $df=75$, $t=4.89$, $p<.001$, 95% CI [7.93,18.85], with a strong effect size of Cohen's $d=1.13$. Contrary to the hypothesis, however, the analysis demonstrated no effect of intervention group on the primary outcome measure. The cLDA model revealed a difference in mean of $diff=.07$ points on the BDI-II ($SE=3.17$, $df=75$, $t=.02$, $p=.984$, 95% CI [-6.26, 6.3], Cohen's $d=.00$) in the psychological intervention group ($n=16$; $M=15.75$, $SD=9.75$) compared with the rtfMRI neurofeedback group ($n=19$; $M=15.68$, $SD=10.02$). Thus, the psychological intervention was shown to be of equal effectiveness in reducing

depressive symptomatology compared with the rtfMRI neurofeedback training as assessed with the BDI-II (Figure II.3).

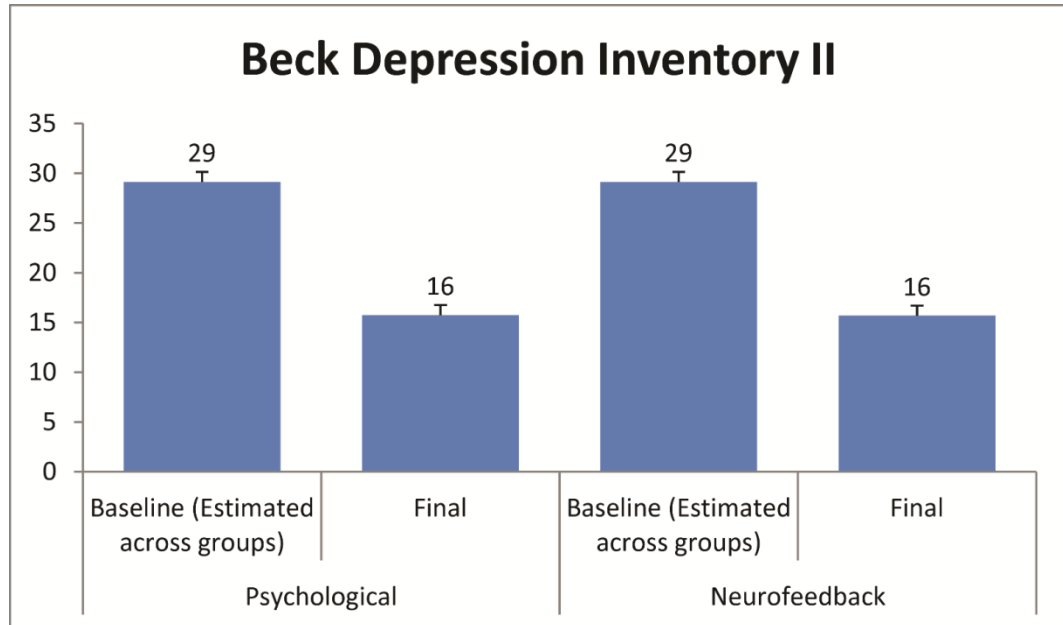


Figure II.3: Pre- vs post-treatment comparison in score means on the BDI-II for the psychological intervention (n=16) and rtfMRI neurofeedback training group (n=19). The cLDA model estimates a common baseline BDI-II score across treatment groups (N=43). Both interventions were shown to be of equal effectiveness, consisting of 56.25% treatment responders in the psychological intervention group vs 57.89% treatment responders in the rtfMRI neurofeedback group. Treatment response was defined as an improvement of $\geq 50\%$ on the defined outcome measure. Figure adapted from Zahn (2018).

II.4.3) Pre-registered outcome measures: secondary outcome measures

Measures of depression, self-esteem and self-blame

Intervention group comparisons on pre-registered secondary outcome measures are presented in Tables II.3, II.4 and II.5. In both intervention groups, there were significant improvements on measures of depressive symptoms, including the QUIDS-SR16 and the depression-dejection subscale of the POMS.

Similarly, participants of both intervention groups showed a substantial reduction in symptoms on observer-rated measures, e.g. the MADRS, on trial completion compared with baseline. Moreover, MDD patients' self-esteem increased significantly post- vs pre-treatment, regardless of the intervention group they had been allocated to. Nevertheless, and inconsistent with the a priori hypothesis, the rtfMRI neurofeedback intervention was not found to be superior over the psychological intervention on any of the pre-registered secondary outcome measures. On all other measures, including observer- and self-rated measures of self-blame (Table II.5), no improvement in symptoms was observed in both treatment groups.

Adverse events and withdrawal rates

Adverse event and withdrawal rates were pre-registered as additional secondary outcome measures. Notably, rtfMRI neurofeedback training, as well as the solely psychological treatment, were found to be safe and feasible forms of intervention. No significant differences emerged regarding adverse events or withdrawal rates throughout the trial following randomisation or specifically, between the first treatment session and trial completion (Table II.4). Overall, six adverse events were reported following randomisation, three occurring at a time point subsequent to the first treatment session. A possible relationship with the study has been suspected in four of the overall six adverse events throughout the trial, while no relationship was observed in one case and a probable relationship was assumed in one other instance. In the latter case, the participant reported transient insomnia lasting one night after his first rtfMRI neurofeedback session.

All adverse events were mild and constituted to two withdrawals and one incident of exclusion from the study. The participant was excluded on the day of the first treatment session, after having been randomised to the psychological intervention group, as the patient presented with symptoms of depression that had worsened by 10 points on the BDI-II between baseline assessment and first intervention day. In addition, one adverse event occurred prior to randomisation and had no relation with the study. The participant's result on the ACE-III was critical, and the participant was advised to consult a specialist for further testing.

Throughout the trial, seven participants withdrew their consent and ended their participation in the study, four prior to the first day of intervention and three at different time points following their first treatment session. In the former instance, participants reported to not feel well enough to participate or to experience time-related challenges that would make it impossible to attend the five scheduled study appointments. In the situation of participants withdrawing after their first treatment session, they described family or financial reasons for their decision. As aforementioned, transient insomnia in the night following the first rtfMRI neurofeedback session was cause for one MDD patient to discontinue trial participation.

Real-time fMRI neurofeedback group: rSATL–posterior SC connectivity post- vs pre-intervention

As a further secondary outcome measure, specific to the rtfMRI neurofeedback intervention group, functional connectivity between the rSATL and the posterior SC was measured for self-blame relative to blaming others, post- vs pre-intervention. Change in functional connectivity was assessed by calculating

regression coefficient means for time series pre- and post-rtfMRI neurofeedback training. As predicted, a significant training-induced reduction in connectivity between the rSATL and posterior SC was detected in the guilt condition relative to indignation by means of a significant time x condition interaction in a repeated measures ANOVA (Table II.6). Inconsistent with the prediction, this decrease was not found to be significant for the guilt condition itself ($t=-.89$, $df=17$, $p=.387$; $n=18$), the mean difference between conditions was -1.27 with a 95% confidence interval between $-.43$ and $.18$. Interestingly, as guilt-specific connectivity successfully reduced relative to indignation post-treatment, indignation-related connectivity between the rSATL and posterior SC was observed to increase with a mean difference of $.09$ post- vs pre-rtfMRI neurofeedback training (Figure II.4; Table II.6). This finding, however, was not significant itself ($t=.68$, $df=17$, $p=.504$, 95% CI $[-1.76, 3.43]$).

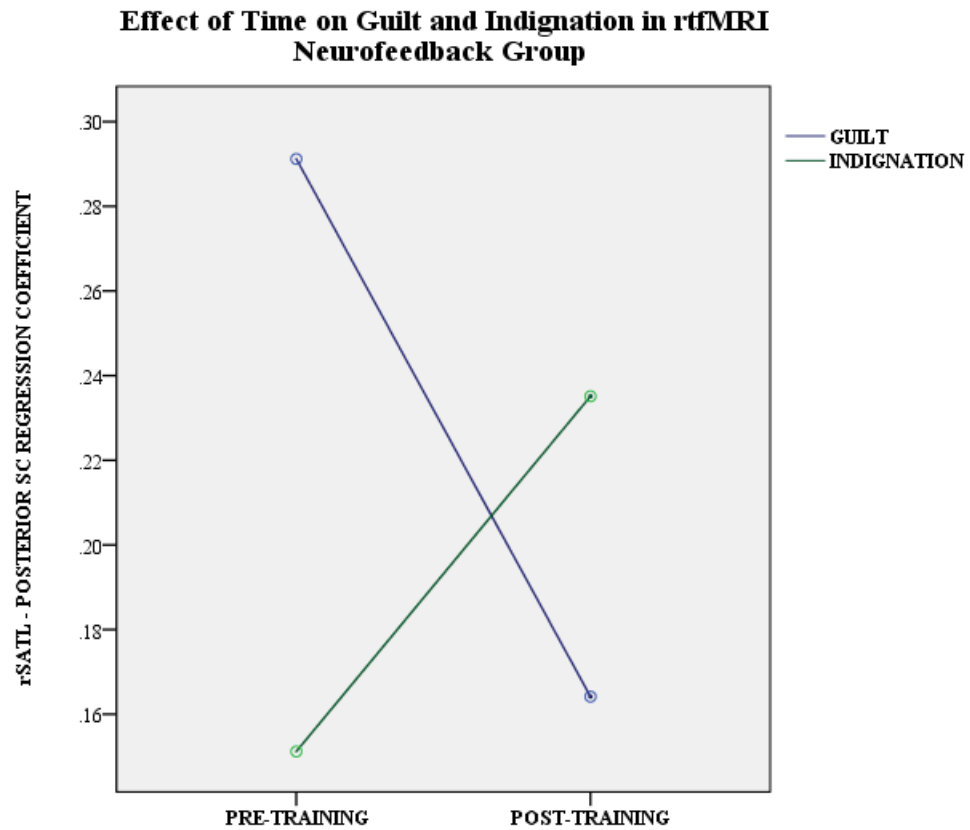


Figure II.4: Relative change in functional connectivity between rSATL and posterior SC in the guilt and indignation condition, measured as Cohen's D for regression coefficient means for time series pre- and post-rtfMRI neurofeedback training, comparing the first and final treatment session.

In addition to applying the CLDA model, the intention-to-treat (ITT) approach was chosen and compared with the per-protocol analyses, using the Pearson Chi-Square test to analyse the association between intervention group and treatment response on the primary outcome measure (BDI-II). The ITT analysis includes data of all randomised participants regardless of their adherence or withdrawal subsequent to randomisation (Fisher et al., 1990). Here, participants who withdrew from the study or did not complete the trial were treated as non-responders. No relationship was found between intervention group and treatment

response $\chi^2(1, N=43)=.029, p=.864$. The estimated treatment effect is considered to be conservative in ITT analysis and caution is raised in terms of ITT's susceptibility to type II errors. The ITT approach might miss proving the efficacy of an actually efficacious therapy (for a review see Gupta, 2011). Contrary to the ITT analysis, the per-protocol analysis risks to falsely present a treatment effect (type I error). It excludes participants who withdraw after randomisation and disregards data of those who do not complete the study. The per-protocol analysis may lead to significant reductions in statistical power by affecting the overall sample size (Gupta, 2011). Using this analysis, no association between intervention group and treatment response was found $\chi^2(1, N=35)=.046, p=.830$. The results of these additional analyses confirm findings based on the cLDA model and were contrary to our predictions.

Throughout all treatment sessions and active neurofeedback runs, participants were able to successfully regulate the neurofeedback thermometer by more than ~50% (Figure II.5). This is remarkable considering that FRIEND implements a moving target algorithm steering to increase the difficulty in controlling the neurofeedback thermometer as connectivity between the rSATL-posterior SC effectively reduces.

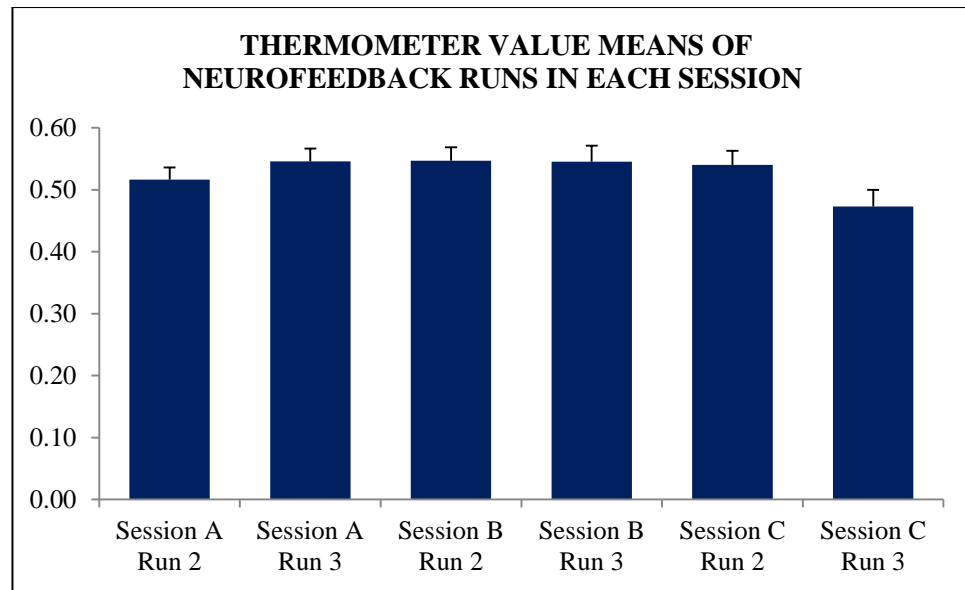


Figure II.5: NF participants were successful in controlling the neurofeedback thermometer by ~50%. Participants' neurofeedback success occurred already in the first session and was stable throughout further sessions with a slight drop in the final active run. FRIEND's moving target algorithm responds to successfully reduced functional rSATL-posterior SC correlations by increasing the difficulty in upregulating the NF thermometer.

A repeated measures ANOVA was conducted to investigate differences in rSATL-posterior SC functional connectivity pre- vs post-intervention in the guilt vs indignation condition over the course of all three treatment sessions. This analysis approach was chosen to contrast the two psychological conditions and thereby control for non-specific correlations, which make up a large fraction of the signal when considering each condition in isolation. While a significant main effect was found for pre- vs post-intervention ($F(1,17)=4.5$, $p=.049$, Wilks' Lambda=.79, $\eta^2=.21$), there was only a trendwise interaction between session and pre- vs post-interventional rSATL- posterior SC connectivity ($F(2,16)=2.79$, $p=.091$, Wilks' Lambda=.74, $\eta^2=.26$). Pre- and post-interventional connectivity measures and their change over the course of all three neurofeedback training

sessions are displayed in Figure II.6. This shows that guilt connectivity was indeed reduced after the neurofeedback training relative to indignation in concordance with our main analysis. It appears that most of this training effect occurred already after the first session (Session A), but this observation was only supported by a trendwise interaction between session and intervention effect.

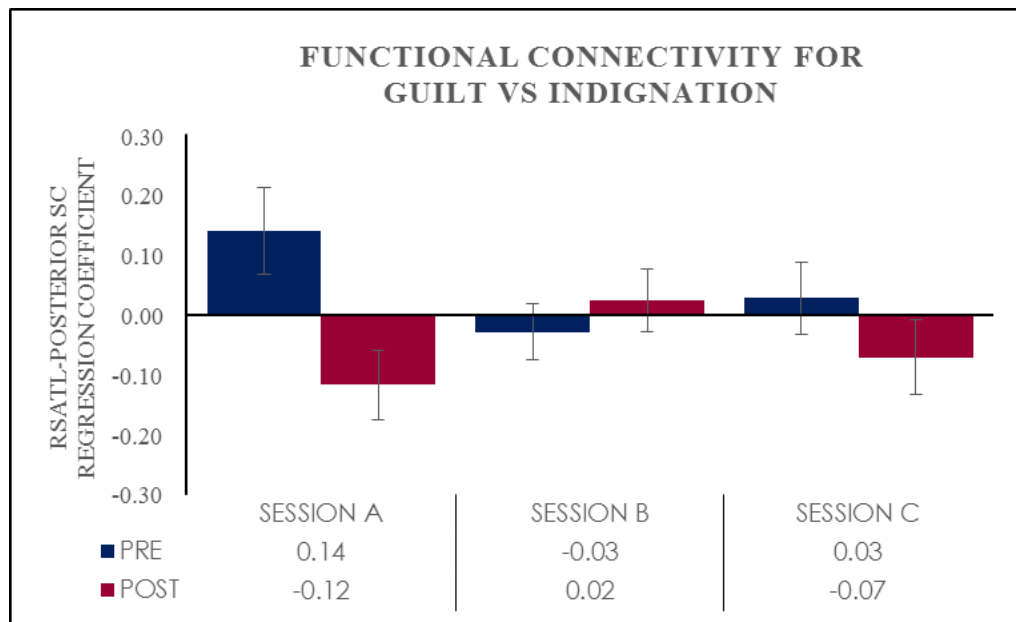


Figure II.6: Change in functional connectivity between rSATL and posterior SC in the guilt vs indignation condition, measured as Cohen's D for regression coefficient means with standard errors for time series pre- and post-rtfMRI neurofeedback training in $n=18$ participants plotted for each neurofeedback session.

There was no difference between non-anxious and anxious distress MDD patients with regard to their functional connectivity between the rSATL and posterior SC for guilt relative to indignation prior to the initial neurofeedback session ($U=35.00$, $N_{\text{MDDnon-anxious}}=6$, $N_{\text{MDDanxious}}=13$, $p=.765$, two-tailed) or after the final neurofeedback training ($U=26.00$, $N_{\text{MDDnon-anxious}}=5$, $N_{\text{MDDanxious}}=13$, $p=.566$, two-tailed). Similarly, no difference between patients groups was found in

the change of functional connectivity between the rSATL and posterior SC in the guilt versus indignation condition pre- versus post-treatment ($U=30.00$, $N_{\text{MDDnon-anxious}}=5$, $N_{\text{MDDanxious}}=13$, $p=.849$, two-tailed).

II.4.4) Exploratory secondary data analysis

Major depressive disorder with and without anxious distress

Based on the primary finding of equally strong treatment responses in both intervention groups, subsequent exploratory data analyses of clinical subtypes of MDD investigated differences in the response of MDD patients with and without anxious distress. This analysis approach was chosen given the prominent frequency of MDD patients of the anxious distress subtype ($n=21$) amongst the completers of the study ($n=35$). Notably, univariate GLM analysis demonstrated the superiority of rtfMRI neurofeedback training in MDD patients without anxious distress relative to the solely psychological intervention, which showed relatively greater effectiveness in MDD patients of the anxious distress subtype ($F(1,30)=4.98$, $p=.033$, $\eta^2=.14$; Figure II.7).

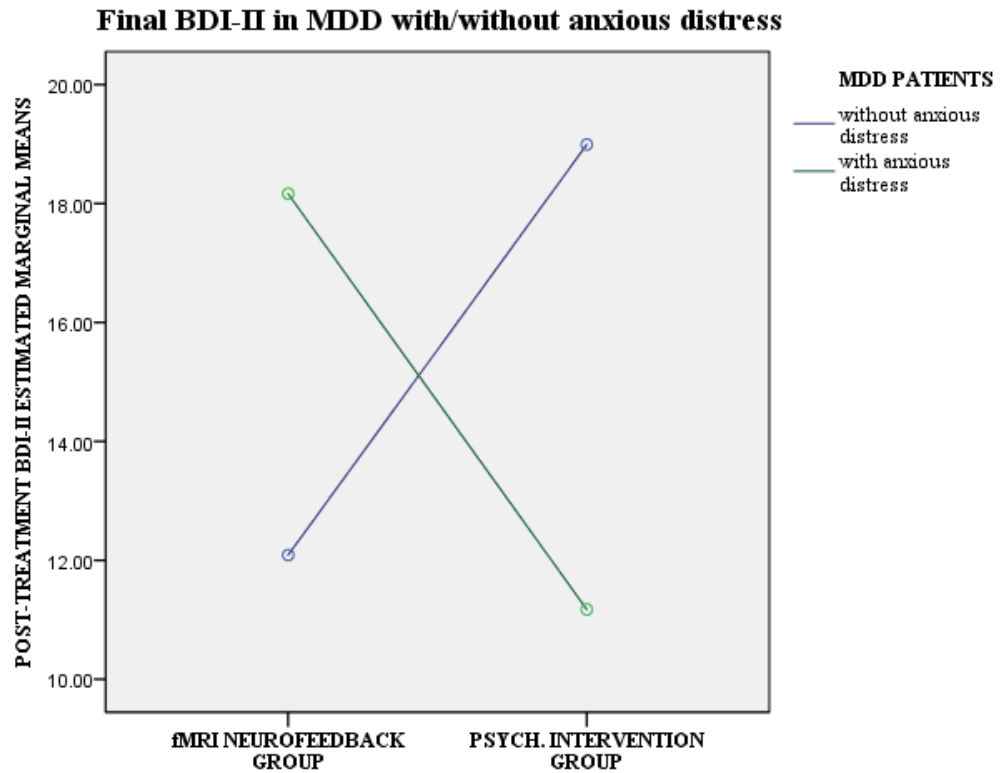


Figure II.7: Post-treatment BDI-II estimated marginal means of MDD patients with and without anxious distress in both treatment groups (rtfMRI neurofeedback group: $n=19$, 13 with, six without anxious distress; psychological intervention group: $n=16$, eight with and eight without anxious distress). In the rtfMRI neurofeedback group, 46.14% MDD patients with anxious distress halved their BDI-II scores post-treatment, compared to 75% responders of the anxious distress subtype in the psychological intervention group. Similarly, 83.33% of patients without anxious distress responded to the rtfMRI neurofeedback training, compared with 37.5% in the psychological intervention group. Covariates appearing in the model are evaluated at the baseline BDI-II value of 28.60 points. There was no significant main effect of the MDD anxious/non-anxious subtype ($F(1,30)=.78$, $p=.782$, $\eta^2=.003$), nor an effect of treatment group ($F(1,30)=0$, $p=.989$, $\eta^2=0$).

Change in connectivity on fMRI, self-esteem and engagement in treatment

Based on previous findings, where measures of self-esteem correlated with changes in functional connectivity between the rSATL and the anterior subgenual SC after rtfMRI neurofeedback training (Zahn et al., 2018), non-parametric

correlation analyses were conducted to explore this pattern in the rtfMRI neurofeedback group (Table II.7). Notably, no such correlation was found, a change in connectivity between the rSATL and the posterior SC in guilt relative to indignation was not associated with an increase in self-esteem in the patient group. Interestingly, however, improvement in depression scores correlated with an increase in self-esteem. Similarly, a positive correlation was found between increased self-esteem and engagement in treatment as assessed by the summed frequency of use of treatment-specific psychological strategies throughout the study in both intervention groups.

Table II.3: Intervention group comparisons on pre-registered secondary outcome measures

MEASURE [sample size]	PRE- INTERVENTION		POST- INTERVENTION		cLDA EFFECT OF TIME								cLDA EFFECT OF GROUP					
	PSYCH&NFB		PSYCH		NFB		BASELINE vs. FINAL						PSYCH vs. NFB					
	M	SD	M	SD	M	SD	diff [df]	SE	p	95% CI	t	d	diff [df]	SE	p	95% CI	t	d
MADRS [PRE: 43; POST: 35]	22.84	6.97	15.56	6.38	14.37	6.55	7.27 [75]	1.98	.00*	3.33 to 11.22	3.68	.85	1.19 [75]	2.29	.60	-3.37 to 5.76	.52	.12
QUIDS-SR16 [PRE: 43; POST: 35]	16.79	6.53	10.88	6.53	10.16	4.41	5.92 [75]	1.67	.00*	2.58 to 9.25	3.53	.82	.72 [75]	1.94	.71	-3.15 to 4.58	.37	.09
POMS 2 Depression- Dejection Scale [PRE: 43; POST: 35]	10.91	4.47	7.81	4.59	7.21	5.67	3.09 [75]	1.41	.03*	.29 to 5.90	2.20	.51	.60 [75]	1.63	.71	-2.65 to 3.85	.37	.09
Rosenberg Self-Esteem Scale [PRE: 43; POST: 35]	20.60	3.49	24.19	4.15	24.58	5.26	-3.59 [75]	1.20	.00*	-5.98 to -1.18	-2.97	-.69	-.39 [75]	1.40	.78	-3.17 to 2.39	-.28	-.06
Implicit Self-Blame Contempt-Anger [PRE: 41; POST: 35]	.00	39.00	-.28	.36	-.05	.39	.29 [73]	.11	.01	.06 to .51	2.53	.59	-.23 [73]	.13	.08	-.49 to .03	-1.8	-.42
Implicit Self-Blame Contempt-Anxiety [PRE: 38; POST: 35]	.32	38.00	.24	.42	.24	.47	.08 [70]	.12	.50	-.16 to .32	.68	.16	.00 [70]	.13	.98	-.27 to .26	-.03	-.01
Agency-Incongruent Self-Blame [PRE: 43; POST: 35]	15.25	16.85	10.76	14.97	10.23	17.59	4.48 [75]	4.88	.36	-5.25 to 14.21	.92	.21	.53 [75]	5.66	.93	-10.7 to 11.80	.09	.02

*=significant at $p=.05$, 2-sided. Between-group Cohen's d scores were computed from t -values and degrees of freedom (Rosenthal & Rosnow, 1991) of the differences between groups. Mean differences and 95% confidence intervals were taken from cLDA models for differences between post- vs pre-training. Implicit self-blame was measured using the BIAT. Agency-incongruent self-blame was measured using the modified version of the VMST. PSYCH = psychological intervention group, NFB =

rtfMRI neurofeedback group. CI = confidence interval, M = mean, SD = standard deviation, SE = standard error, diff = difference of means, df = degrees of freedom, d = Cohen's d.

Table II.4: Intervention group comparisons on pre-registered secondary outcome measures (cont.)

MEASURE [sample size]	MANN- WHITNEY U	ASYMP. SIG.	EXACT SIG.	MEDIAN		RANGE		MINIMUM		MAXIMUM	
				PSYCH	NFB	PSYCH	NFB	PSYCH	NFB	PSYCH	NFB
Observer-Rated CGI Post-Intervention [35; NFB: 19; PSYCH: 16]	129.00	.376	.461	2.00	2.00	2.00	3.00	2.00	2.00	4.00	5.00
Participant-Rated CGI Post-Intervention [35; NFB: 19; PSYCH: 16]	139.50	.658	.683	2.50	2.00	4.00	4.00	1.00	1.00	5.00	5.00
Withdrawal Rates throughout trial [43; NFB: 22; PSYCH: 21]	218.50	.635		0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
Withdrawal Rates after first treatment session [43; NFB: 22; PSYCH: 21]	221.00	.582		0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
Adverse Events throughout trial [43; NFB: 22; PSYCH: 21]	208.00	.352		0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00
Adverse Events after first treatment session [43; NFB: 22; PSYCH: 21]	219.50	.527		0.00	0.00	1.00	1.00	0.00	0.00	1.00	1.00

Asymp. Sig.= 2-tailed; Exact Sig.= 2*(1-tailed Sig.). PSYCH = psychological intervention group, NFB = rtfMRI neurofeedback training group.

Table II.5: Intervention group comparisons on pre-registered secondary outcome measures (cont.)

MEASURE [sample size]	PRE-INTERVENTION						POST-INTERVENTION						GENERALIZED LINEAR MODEL ORDINAL LOGISTIC					
	PSYCH			NFB			PSYCH			NFB			EFFECT OF GROUP			EFFECT OF TIME		
	Mdn	Min	Max	Mdn	Min	Max	Mdn	Min	Max	Mdn	Min	Max	Wald Chi-Square	df	p	Wald Chi-Square	df	p
Participant-Rated Self-Blame [PRE:39; POST:35]	8.5	7.0	10.0	8.5	4.5	10.0	5.0	2.0	9.0	4.0	1.0	9.0	.00	1.00	1.00	4.20	9.00	.90
Observer-Rated Self-Blame [PRE:43; POST:35]	2.0	.0	7.0	2.0	.0	7.0	1.0	.0	4.0	1.0	.0	5.0	.00	1.00	1.00	11.81	7.00	.11

Participant-rated self-blame scores are based on the mean of two autobiographical events per subject; Observer-rated self-blame scores are based on the moral emotion addendum of the AMDP Psychopathology Interview questions on depression (Faehndrich & Stieglitz, 1997). PSYCH = psychological intervention group, NFB = rtfMRI neurofeedback group. Mdn = Median, Min = Minimum, Max = Maximum, df = degrees of freedom.

Table II.6: Post-training vs pre-training comparison of pre-registered secondary outcome measure rSATL – posterior SC correlation on fMRI

MEASURE [sample size]	PRE-TRAINING		POST-TRAINING		REPEATED MEASURES ANOVA					
	NFB		NFB		TIME		CONDITION		TIMExCONDITION	
	M	SD	M	SD	F	p	F	p	F	p
Guilt: rSATL-SC regression effect [n=18]	.29	.54	.16	.37	.29	.87	.43	.52	6.40	.02*
Indignation: rSATL-SC regression effect [n=18]	.15	.46	.24	.25						

*=significant at p=.05, 2-sided. NFB = rtfMRI neurofeedback group, rSATL-SC = right superior anterior temporal lobe - posterior subgenual cortex.

Table II.7: Secondary correlation analyses

			Rosenberg difference score [post-pre]	BDI-II reduction in percent [post-pre]	Frequency of strategy use since visit 2	rSATL-SC connectivity, difference in Cohen's d, guilt vs indignation[post-pre]	rSATL-SC connectivity, difference in Cohen' s d, guilt [post-pre]
Spearman's rho	Rosenberg difference score [post-pre]	Correlation Coefficient	1.000	-.702**	.385*	0.197	0.225
		Sig. (2-tailed)		0.000	0.022	0.434	0.370
		N	35	35	35	18	18
	BDI-II reduction in percent [post-pre]	Correlation Coefficient	-.702**	1.000	-0.241	-0.182	-0.214
		Sig. (2-tailed)	0.000		0.164	0.470	0.394
		N	35	35	35	18	18
	Frequency of strategy use since visit 2	Correlation Coefficient	.385*	-0.241	1.000	0.260	0.048
		Sig. (2-tailed)	0.022	0.164		0.298	0.850
		N	35	35	35	18	18
	rSATL-SC connectivity, difference in Cohen's d, guilt vs indignation [post-pre]	Correlation Coefficient	0.197	-0.182	0.260	1.000	.472*
		Sig. (2-tailed)	0.434	0.470	0.298		0.048
		N	18	18	18	18	18
	rSATL-SC connectivity, difference in Cohen' s d, guilt [post-pre]	Correlation Coefficient	0.225	-0.214	0.048	.472*	1.000
		Sig. (2-tailed)	0.370	0.394	0.850	0.048	
		N	18	18	18	18	18

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed). Difference scores were computed by subtracting post- vs pre-treatment scores.

II.5.) Discussion

II.5.1) Discussion of main findings

This single-blind, randomised, controlled proof-of-concept trial investigated the clinical benefits of a novel rtfMRI neurofeedback protocol compared to the therapeutic effects of a newly designed self-guided psychological intervention in current and insufficiently remitted MDD. It was hypothesised that patients randomised to the rtfMRI neurofeedback group show a reduction in depressive symptoms and self-blame while exhibiting an increase in self-worth compared to the psychological intervention group. Furthermore, it was proposed that patients undergoing rtfMRI neurofeedback training show a decreased functional connectivity between the rSATL and the posterior SC post-treatment compared to pre-treatment. Decreased functional connectivity between the rSATL and posterior SC region was predicted to be associated with a reduction in depressive symptoms in the rtfMRI neurofeedback group.

The results demonstrated that both interventions proved to be safe for MDD patients, with no relevant adverse events occurring in either group. There was a strong effect size for patients' improvement on self-rated and observer-rated depression measures with response rates above 55% in both intervention groups. Thus, the safety and overall clinical benefits of the rtfMRI neurofeedback intervention in MDD is in keeping with previous studies (Linden et al., 2012, Mehler et al., 2018, Young et al., 2014, Young et al., 2017a). This is particularly remarkable as the NeuroMooD protocol asked participants to engage with negative rather than positive emotions, opposed to previous studies (Linden et al., 2012, Mehler et al., 2018, Young et al., 2014, Young et al., 2017a). Contrary to

the first hypothesis, no difference was found between the rtfMRI neurofeedback and the psychological intervention group on the primary outcome measure (BDI-II). The second prediction was confirmed as the rtfMRI neurofeedback training resulted in a decrease in functional connectivity between the rSATL and the posterior SC for guilt relative to indignation. Contrary to the third hypothesis, no relationship was found between connectivity changes and the changes in depressive symptoms after three sessions of rtfMRI neurofeedback training.

Various considerations need to be taken into account as to why no group differences were found on primary and secondary outcome measures. One possibility might be that the improvements observed in both intervention groups were due to spontaneous remission or placebo-like effects instead of being the result of the experimental treatment. This is possible, yet unlikely to be the only explanatory factor for this finding as the placebo response rate in MDD is generally found to be lower, usually around 30% (Walsh, Seidman, Sysko & Gould, 2002), well below the >55% response rate demonstrated in both treatment groups in the NeuroMooD trial. Furthermore, the NeuroMooD protocol aimed at minimising the risk of including spontaneously remitting patients by including MDD patients only if they were stable, i.e. with no improvement, in symptoms for at least six weeks before randomisation into the study, and by restricting inclusion to patients with early treatment-resistance and recurrent MDD. Lastly, the frequency of how often participants used the psychological strategies between treatment visits was found to positively correlate with an increase in self-esteem in both intervention groups, which further argues against spontaneous remission as an explanation for the observed findings. Another possible explanation as to why rtfMRI neurofeedback did not show superiority

over the psychological intervention might be because the rtfMRI neurofeedback intervention provided no added value in reducing symptoms of depression in early treatment-resistant MDD compared with the strong effects of the self-guided psychological intervention. While this explanation cannot be ruled out, the secondary data analysis suggests that rtfMRI neurofeedback training is superior to the psychological intervention in the non-anxious distress subtype of MDD. This finding will, however, require further confirmation in future studies.

The observed rtfMRI neurofeedback training-induced reduction in functional connectivity between the rSATL and the posterior SC for guilt relative to indignation demonstrates that MDD patients were able to successfully modulate their brain connectivity as guided by the rtfMRI neurofeedback signal. The lack of association between functional connectivity changes and improvement in the severity of depressive symptoms is in keeping with the limited clinical benefit in the rtfMRI neurofeedback group overall. Considering that the majority of MDD patients in the rtfMRI neurofeedback group were of the anxious distress subtype ($n=13$ vs $n=6$ non-anxious MDD), the neural fMRI target may be irrelevant for the anxious distress subtype of MDD; a hypothesis that will be further examined in the next chapter.

II.5.2) Limitations

The following potential limitations of the NeuroMooD trial need to be considered: firstly, the study might have been underpowered and, therefore, unable to detect a clinically meaningful difference between the two intervention groups. Nevertheless, the effect sizes for non-superiority of the rtfMRI neurofeedback group were so small, that even a large sample would have been

unable to find differences between groups. Furthermore, the trial's sample size was comparable to other randomised clinical trials investigating rtfMRI in MDD (Mehler et al., 2018; Young et al., 2017a). Young et al. (2017a) found a symptom reduction of more than 50% in the rtfMRI neurofeedback group compared to 8% in the control group as assessed one week after the completion of two amygdala-targeting rtfMRI neurofeedback sessions. A further limitation of the NeuroMood trial might consist in the heterogeneity of the sample with the inclusion of only few MDD patients of the non-anxious distress subtype and the inclusion of participants with current or past diagnoses of anxiety and trauma-related disorders, i.e. past PTSD with residual symptoms and current and past social anxiety disorder.

Contrary to previous rtfMRI neurofeedback studies in MDD (Young et al., 2014, Young et al., 2017a) that included medication-free patients, the majority of MDD patients participating in the NeuroMood trial were taking antidepressant medication. Interactions of NeuroMood interventions with medication effects cannot be out ruled as only 56% of participants were taking antidepressant medications in the psychological intervention group compared to 84% in the rtfMRI neurofeedback group. Despite the possibility that antidepressant medication may have negatively impacted on the participants' performance during the rtfMRI neurofeedback training, Linden et al.'s, (2012) pioneering rtfMRI neurofeedback study targeted a sample on stable antidepressant medication comparable to NeuroMood and demonstrated the superiority of the rtfMRI neurofeedback relative to the control condition. Finally, and opposite to Young et al. (2017a), the NeuroMood study was limited by lacking a rtfMRI neurofeedback control arm. Notably, however, Young et al. (2017a) used the left

intraparietal sulcus for the neurofeedback signal in the control condition which is not involved in the processing or recall of positive emotions, which might have interfered with the positive psychological effects of their control intervention.

II.5.3) Conclusion

Both interventions were demonstrated to be safe and resulted in a reduction in symptom severity of 46% and a treatment response of more than 55% in the study sample of current and insufficiently remitted, early treatment-resistant MDD. Albeit some contribution of placebo-like effects cannot be ruled out, it is likely that the self-guided psychological intervention has demonstrated beneficial effects. Self-blame specific rtfMRI neurofeedback training may be more effective than the psychological intervention in MDD patients without anxious distress, which needs further confirmation in future studies.

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Chapter III: Self-blaming biases and distinctive clinical features of major depressive disorder with and without anxious distress

III.1) Abstract

Major depressive disorder (MDD) is frequently accompanied by prominent symptoms of anxiety, which is reflected in the introduction of the anxious distress subtype of MDD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Research suggests that there is evidence for substantial differences between anxious and non-anxious MDD. The work presented in this chapter refers back to findings discussed in chapter II and explores self-blaming biases and distinct clinical characteristics of anxious and non-anxious MDD patients, in order to better understand the differential response of both patient groups to the clinical interventions in the NeuroMood trial.

It was hypothesised that MDD with anxious distress would be associated with higher levels of stressful life events and anger towards others, resulting in reduced self-blaming emotional biases. These predictions were partly confirmed. MDD patients with anxious distress showed elevated levels of anger and hostility on some, but not all measures, compared with non-anxious MDD patients and healthy control (HC) participants. Also, the anxious MDD subtype did not differ on measures of early life trauma but was found to have experienced past stressful life events more frequently. MDD groups did not differ on any other clinical measures. Notably, anxious and non-anxious MDD failed to show self-blaming biases on the experimental measure, the modified version of the value-related moral sentiment task (VMST), despite 70% of patients expressing at least moderate levels of self-blame when clinically assessed. The results suggest that

self-blaming emotional biases in interpersonal situations, as measured on our experimental task, may only be relevant for some but not all subgroups of MDD. Further, the current findings highlight the need for the development of additional experimental measures to capture self-blaming biases in other contexts, such as when personal achievement is concerned.

III.2) Introduction

III.2.1) Background: anxious depression and MDD with anxious distress

Major depressive disorder (MDD) is found to be frequently accompanied by prominent symptoms of anxiety or comorbid with anxiety disorders (Schaffer et al., 2012). Gaspersz et al. (2018) discern that the term ‘anxious depression’ is commonly used to characterise three distinct anxiety-depression profiles: MDD with a comorbid anxiety disorder, MDD with anxiety symptoms above a cut-off score on an anxiety measure, and lastly, MDD with anxious distress, as assessed according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association [APA], 2013).

Researchers and clinicians distinguish anxious depression from non-anxious depression due to substantial evidence on their differences, which are of clinical relevance. Not only is anxious depression very common (45.1-78%, Fava et al., 2006; Lamers et al., 2011; Zimmerman et al., 2017), but MDD patients with anxiety symptoms or comorbidities are found to have more severe and chronic courses of MDD (Fava et al., 2004; Fava et al., 2006; Goldberg & Fawcett, 2012; Rhebergen et al., 2011), poorer treatment response (Domschke, Deckert, Arolt, & Baune, 2010; Farabaugh et al., 2012; Fava et al., 2008; Ionescu, Niciu, Richards, & Zarate, 2014), higher rates of self-harm, suicidal ideation and suicide attempts (Fava et al., 2004; Fawcett, 2001; Goldberg & Fawcett, 2012) and lower quality of life and functioning (Chan et al., 2012) compared with non-anxious MDD patients. Furthermore, differences seem to exist in the neurobiology of their illness, including cortical thinning, functional connectivity abnormalities and

immune response anomalies (Gaspersz et al., 2017c; Ionescu, Niciu, Mathews, Richards, & Zarate, 2013; Shim, Woo, & Bahk, 2016).

Ultimately, the DSM-5 Mood Disorders Workgroup introduced and defined the MDD anxious distress specifier in DSM-5 (APA, 2013) which acknowledges the anxiety-dominant subpopulation in MDD. The DSM-5 anxious distress specifier consists of five items, capturing the presence of at least two of five symptoms during the majority of days of a major depressive episode (MDE): (1) feeling keyed up or tense, (2) feeling unusually restless, (3) having difficulties concentrating because of worrying, (4) feeling afraid that something awful may happen, (5) feeling that anxiety or worry would be out of control. In addition, the severity of anxious distress can be assessed, ranging from mild (two symptoms present) to severe (four or five symptoms present, with psychomotor agitation).

Recent studies confirmed the reliability and validity of the anxious distress specifier (Gaspersz et al., 2017b; Zimmerman et al., 2014; Zimmerman et al., 2017) and demonstrated the prevalence of the anxious distress subtype in MDD to be ranging from 54.2 % to 78% (Gaspersz et al., 2017a, Gaspersz et al., 2017b; McIntyre et al., 2016; Zimmerman et al., 2017). Post-hoc analyses found MDD patients of the anxious distress subtype to be suffering from a greater severity of MDD, higher rates of cognitive and functional impairment and increased suicidal ideation compared with non-anxious MDD (Maneeton et al., 2017; McIntyre et al., 2016; Zimmerman et al., 2014). In addition, patients with anxious distress endure a lower quality of life and profound insomnia (Maneeton et al., 2017; McIntyre et al., 2016). Gaspersz et al. (2018) concluded that the DSM-5 MDD anxious distress specifier captures a highly prevalent, clinically distinct and relevant subgroup of MDD patients who are characterised by a poorer clinical

response and treatment outcome and who are not identified otherwise, as research shows that the anxious distress subtype overlaps only poorly with DSM-IV anxiety disorders (Gaspersz et al., 2017b). Rosellini (2018) points to higher co-morbidity rates with anxiety disorders such as generalised anxiety disorder (GAD).

As outlined within the previous chapter of this thesis, MDD patients of the anxious distress subtype outweighed the number of non-anxious MDD patients in the NeuroMooD study. Considering the literature presented, this observation is not surprising, as the recruitment for NeuroMooD was targeted at MDD patients with at least some degree of treatment resistance. Interestingly, patients with and without anxious distress showed differences in their treatment response to the rtfMRI neurofeedback training and psychological intervention, which both aimed at addressing self-blaming biases in MDD.

To my knowledge, no studies of self-blaming emotions or biases in MDD patients with anxious distress have been published at present, while there is some evidence for a weak association with anger in this MDD subtype (Zimmerman et al., 2014; Zimmerman et al., 2017). Furthermore, post-hoc analyses found symptoms of anxious distress in MDD to be co-occurring with irritability (i.e. the feeling of general frustration and annoyance) and decreased response to antidepressant treatment (Brown, DiBenedetti, Danchenko, Weiller, & Fava, 2016).

As it becomes apparent, evidence on the cognitive and clinical characteristics of the DSM-5 MDD anxious distress subtype is still scarce. This chapter serves the aim to explain the differences observed in anxious and non-

anxious MDD patient groups in their response to the treatment of self-blaming emotional biases in the NeuroMooD study, as presented in chapter II.

III.2.2) Background: self-blaming emotional biases in MDD

Self-blaming emotions are a frequently observed characteristic of MDD (Sartorius, Jablensky, Gulbinat, & Ernberg, 1980). Retrospective assessment of past MDEs in MDD revealed self-blaming emotions to be occurring in more than 80% of MDD patients during their most severe MDE (Zahn et al., 2015b).

Freud (1917) was the first to recognise excessive self-blame to be distinctive for MDD. Among modern psychological models, Abramson et al.'s (1978) revised learned helplessness model focusses on self-blaming biases most prominently, postulating that biases towards self-directed blame for failure are substantial in the vulnerability and development of MDD. The model posits the manifestation of such biases in hopelessness, feelings of depression and poor self-worth. The revised learned helplessness model is in contrast to the widely acknowledged view that MDD is due to 'negative affectivity', i.e. an increase in negative emotions in general, alongside with a reduction in positive emotions (Watson, Clark, & Carey, 1988).

There is evidence in support of the revised learned helplessness model as recent studies demonstrate excessive self-blaming emotions, i.e. self-directed guilt, shame, and disgust/contempt towards oneself, to be a prominent characteristic even in remitted MDD (Green, Moll, Deakin, Hulleman, & Zahn, 2013). Contrary to the theory of an overall increase in negativity in MDD, however, negative emotions towards others, i.e. indignation and anger, disgust/contempt towards others, are found to be reduced (Green et al., 2013;

Zahn et al., 2015a). These findings provide further evidence for attributional models of MDD that propose an increase in relative self-blaming emotions to occur as well as a relative diminishment of other-blaming emotions in MDD (Weiner, 1985). Green et al. (2013) and Zahn et al. (2015a) were the first to assess self-directed blame relative to other-blame in MDD while controlling for negative valence, by using an experimental task, the VMST, instead of standardised questionnaires.

Although Zahn et al. (2015b) found self-contempt/disgust to be more prominent in MDD compared to guilt and shame, standard clinical assessments are often limited to measuring (excessive) guilt. The DSM-5 acknowledges inappropriate guilt to be a core symptom of melancholic MDD but does not assess other self-blaming emotions.

Characteristics of shame and guilt and their link to MDD psychopathology have been discussed extensively in the literature, revealing opposing views on the depressogenic nature of these emotions. Tangney et al. (1991; 1992) view guilt as a form of behavioural self-blame concerning a distinct action or behaviour. In this view, guilt is considered to be adaptive and not necessarily associated with poor psychological adjustment (Tangney, Stuewig, & Mashek, 2007). Further, the authors argue that shame, however, reflects a global form of self-blame, devaluating and scrutinising the entire self and resulting in feelings of worthlessness, therefore being associated more closely with MDD psychopathology (Tangney, 1991; Tangney et al., 2007; Tangney et al., 1992).

Contrary to this viewpoint, O'Connor and colleagues propose that guilt can inherit a characterological quality in that as excessive empathy can give rise

to maladaptive forms of guilt (Lynn E. O'Connor, Berry, & Weiss, 1999; L. E. O'Connor, Berry, Weiss, & Gilbert, 2002; O'Connor, Berry, Lewis & Stiver, 2011). Using the Interpersonal Guilt Questionnaire (IGQ-67; O'Connor, Berry, Weiss, Bush & Sampson, 1997), a measure of characterological guilt, the authors found survivor guilt to be highly associated with MDD (O'Connor et al., 1997, O'Connor et al., 1999, O'Connor et al., 2002) and maladaptive attributional styles, such as 'blaming oneself for the misfortune of others' or 'being incapable of taking credit for own successes' (O'Connor et al., 2011).

Various studies in MDD have found evidence in support of the relevance of characterological self-blame (e.g. shame, self-contempt, self-disgust) over behavioural self-blame (i.e. guilt) (Tangney et al., 1992; Tilghman-Osborne, Cole, Felton, & Ciesla, 2008), while other findings demonstrated an increase of both, guilt- and shame-proneness in MDD (Alexander, Brewin, Vearnals, Wolff, & Leff, 1999; Berrios et al., 1992; L. E. O'Connor et al., 2002). Green et al. (2013) conclude that the contradiction in findings may be caused by inconsistencies in the definition of these self-conscious emotions, in addition to being due to differences in how these emotions were operationalised.

It is noteworthy that Tangney & Dearing (2002) found individuals to be performing poorly at distinguishing guilt and shame, which is why the Test of Self-Conscious Affect (TOSCA-3) focuses on action tendencies rather than subjective emotional qualities (Tangney & Dearing, 2000). Action tendencies are thought to be reflective of particular emotions, hence, function as a proxy for them (Tangney et al., 2000).

The study presented in this chapter employed the concept of action tendencies (Roseman, Wiest, & Swartz, 1994) by implementing action tendencies in the VMST, thereby modifying previous versions of this experimental task (Green et al., 2013; Zahn et al., 2015a; Zahn et al., 2009). The aim was to assess subjective emotional qualities and action tendencies with one instrument.

The specific action tendencies implemented in the modified VMST include: 1) feeling like creating distance from oneself, 2) hiding, 3) apologising, 4) creating a distance from one's friend and 4) verbally or physically attacking/punishing one's friend. These action tendencies corresponded to the moral sentiments entailed in the VMST, i.e. guilt, shame, contempt/disgust towards self and others, and indignation/anger towards others.

Feeling like hiding is classically thought to be associated with shame (Tangney & Dearing, 2000), whereas attacking or punishing others is thought to be linked to anger. Creating a distance from oneself or others is thought to be reflective of disgust, based on existing literature that finds moral disgust to be associated with withdrawing from others rather than approaching tendencies as entailed in anger (Haidt et al., 2003; Zahn, De Oliveira-Souza & Moll, 2013). Apologising was included as an action tendency in the modified VMST as it classically is associated with adaptive forms of guilt (Haidt et al., 2003; Tangney & Dearing, 2000; Tangney, Wagner & Gramzow 1989).

As predicted by the authors, Green et al. (2013) found the guilt measure on the VMST to capture non-depressogenic forms of self-blame rather than overgeneralised forms or characterological guilt. Further, guilt on the VMST was demonstrated to be selectively correlating with TOSCA-guilt, but not with the

shame measure on the TOSCA-3. TOSCA-shame, in turn, was found to be associated with the self-contempt measure on the VMST (Green et al., 2013).

The rationale for using the (modified) VMST for the research question presented in this chapter, was based on previous studies that found the VMST to be successful in capturing proneness to experiencing self- and other-blaming emotions in remitted MDD (Green et al., 2013; Zahn et al., 2015a) as outlined above. The VMST measures self-contempt bias by subtracting the percentage of contempt/disgust experienced towards others from the percentage of self-directed contempt/disgust. Specifics of this task will be further explained in section III.3.7.

III.2.3) Specific aims and hypotheses

This chapter aims to identify the differences between anxious and non-anxious MDD patients in relation to self-blaming emotional biases and clinical characteristics.

The following hypotheses were postulated:

Hypothesis 1: MDD patients with anxious distress show higher indignation/anger towards others as compared with MDD patients with non-anxious MDD.

Hypothesis 2: Self-blaming emotional biases will be more pronounced in MDD patients without anxious distress than MDD patients with anxious distress.

Hypothesis 3: MDD patients with anxious distress have experienced stressful life events more frequently than MDD patients without anxious distress.

III.3.) Methods

III.3.1) Study design

Data for this research was collected as part of ‘The cognitive architecture of blame biases study’, (study 2) of the NeuroMooD protocol, which received ethical approval by the NHS Health Research Authority, NRES Committee London – Camberwell St Giles (REC reference: 15/LO/0577).

This case-control study aimed at exploring self-blaming emotional biases in MDD compared with HC participants. Based on findings obtained from the NeuroMooD trial (see chapter II), hence, the differences observed between MDD with and without anxious distress regarding treatment response, this research focused on comparing self-blaming biases and clinical features of anxious and non-anxious MDD patients with HC participants.

III.3.2) Recruitment and reimbursement of participants

MDD patients were recruited, screened and clinically assessed as part of their participation in the NeuroMooD trial. For details on recruitment and assessment procedures and reimbursement, refer to chapter II.3. HC participants were recruited through study adverts, which were posted online or disseminated via university recruitment circulars. HC participants received compensation for the time taken to participate in the study in the form of shopping vouchers worth £20 if included in the study, and £10 if excluded after an initial clinical assessment.

III.3.3) Eligibility assessment

All participants underwent an initial phone screening interview, giving oral consent before formal evaluation. If initial inclusion criteria were met, participants were invited to attend a clinical assessment visit to confirm the eligibility of their participation. Volunteers received a formal invitation via email at least 24 hours before their study visit, providing volunteers with the participant information sheet and study consent form. Where inclusion criteria were met, participants proceeded with the completion of all tasks, tests, and questionnaires. For details of study procedures and measures used, see sections III.3.6, III.3.7 and III.3.8. MDD patients and HC participants underwent identical assessment procedures.

A total of 85 HC participants were screened over the phone and consequently, 21 volunteers were seen for a clinical assessment to confirm eligibility. Following this assessment, 18 HC participants were included in the study and completed all assessments.

For details on recruitment and assessment of MDD patients, please see chapter II.3.3-II.3.7. Participants who could not be included in the NeuroMood study but fulfilled criteria for ‘The cognitive architecture of blame biases study’ were offered to participate. Data of n=49 MDD patients was acquired for this research, 33 MDD patients of the anxious distress subtype, 16 MDD patients without anxious distress.

III.3.4) Inclusion criteria

MDD patients meeting the following criteria were considered for inclusion into the study:

- i. Recurrent MDD according to DSM-5 with at least one MDE of at least two months duration, currently experiencing an MDE or being insufficiently remitted for at least six weeks, with significantly bothering or impairing symptoms (Psychiatric Status Rating of 3-5)
- ii. If treated with antidepressants, on a stable dose for at least six weeks prior to participating and planning to stay on this dose for the duration of the study
- iii. Patients have insufficiently responded to at least one course of cognitive behavioural therapy (CBT) or antidepressants or are not amenable to these standard treatments. MDD patients are not currently undergoing psychotherapy.
- iv. Age range: 18 or older
- v. Right-handedness
- vi. Proficiency in English

HC participants were age- and education-matched to the MDD study population, proficient in English language and right-handed. Importantly, HC participants had no current or history of psychiatric or neurological disorders.

III.3.5) Exclusion criteria

Participants were not eligible for inclusion if any of the following criteria applied:

- i. History of learning disabilities or developmental disorders

- ii. Impairments of vision or hearing which cannot be corrected during the experiment
- iii. History of manic or hypomanic episodes, of schizophreniform symptoms or schizophrenia, or substance abuse, neurological disorders such as seizures, loss of consciousness following brain injury or medical disorders affecting brain function, blood flow or metabolism
- iv. Current intake of benzodiazepines, GABAergic or benzodiazepine receptor agonists
- v. Current recreational drug use
- vi. Pregnancy

In addition to the above criteria, HC participants were excluded if they had a family history of MDD, bipolar disorder, schizophrenia or psychosis, a history of psychiatric disorders themselves or past use of psychotropic medications.

MDD patients, on the other hand, were excluded if they had received a specialist diagnosis of attention deficit hyperactivity disorder (ADHD) or personality disorder or showed significant impairment of psychosocial functioning with at least moderate impairment outside their MDEs as a sign of a possible co-morbid personality disorder.

III.3.6) Clinical assessment

Clinical and experimental, neuropsychological testing occurred in accordance with the NeuroMooD protocol as outlined in detail in chapter II.3 and summarised below. Diagnostic, clinical and cognitive assessment constituted of

standardised, validated measures in addition to the conduction of a non-structured clinical interview and the notion of the participant's medical history. In MDD patients, age at MDD onset and total illness duration was documented, along with details about the course of illness, i.e. number of episodes and episode duration(s).

Summary of standard clinical and cognitive instruments:

- i. Structured Clinical Interview (SCID) for DSM-5 (First, 2015)
- ii. AMDP Psychopathology Interview questions on depression (Faehndrich & Stieglitz, 1997)
- iii. Longitudinal Interval Follow-Up Evaluation (LIFE; Keller et al., 1987)
- iv. Clinical Global Impression (CGI-) Scale (Busner & Targum, 2007)
- v. Beck Depressive Inventory (BDI-II; Beck et al., 1996)
- vi. Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)
- vii. Quick Inventory of Depressive Symptomatology (QUIDS-SR16; Rush et al., 2003)
- viii. Hypomania Checklist-16 (Forty et al., 2010)
- ix. Rosenberg Self-Esteem Scale (Rosenberg, 1965)
- x. Profile of Mood States (POMS) Scale (McNair, Lorr & Dropplemen, 1971)
- xi. MINI International Neuropsychiatric Interview (module on suicidality only; Sheehan et al., 1998)
- xii. Psychiatric Family History Screen (Weissman et al., 2000)
- xiii. Life Events Questionnaire (Brugha & Conroy, 1985)
- xiv. Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998)

- xv. Altman Self-Rating Mania Scale (Altman, Hedeker, Peterson & Davis, 1997)
- xvi. Addenbrooke's Cognitive Examination (ACE-III; Hsieh, Schubert, Hoon, Mioshi & Hodges, 2013) in patients >50 years only

A consultant psychiatrist assessed patients' scores on the AMDP, LIFE, MADRS, CGI, Global Assessment Functioning (GAF) Scale and Social and Occupational Functioning Assessment Scale (SOFAS). I conducted all other parts of the clinical and neuropsychological assessment, after having received extensive training prior to the start of the study supervised by a consultant psychiatrist. Assessment of HC participants was conducted solely by me. Data collection occurred in the absence of adverse events.

III.3.7) Experimental neuropsychological testing: value-related moral sentiment task

MDD patients and HC participants completed experimental tasks that had been developed by our research group, aiming at investigating neurocognitive underpinnings of self- and other-blaming emotions. For a full list of tasks, refer to chapter II.3.8.

Of particular interest for this study was the administration of a modified version of the VMST, a computerised task, investigating emotions related to self-blame (i.e. guilt, shame, self-contempt, self-disgust, self-directed anger) vs blaming others (indignation, anger, disgust, disgust or towards others). The VMST is based on normative data (Zahn et al., 2007; Zahn et al., 2009) and has been validated in previous studies (Green et al., 2013; Pulcu et al., 2014; Zahn et

al., 2009). Markedly, the modified version of the VMST contains a reduced number of stimuli (36 items, 50% self-agency, 50% other-agency) compared to the original version of the VMST (90 items; Zahn et al., 2015a; Zahn et al., 2009), yet implements an added response category related to action tendencies (Roseman et al., 1994). These action tendency categories have previously been validated (Lythe et al., 2015 unpublished data).

The VMST presents participants with hypothetical scenarios of social behaviours in which either the participant (in the self-agent condition) or the participant's best friend (in the other-agent condition) act contrary to social and moral values (see Figure III.1 and Figure III.2). Participants are instructed to select the strongest emotion they would most likely experience in the given unpleasant hypothetical situation (guilt, shame, contempt/disgust towards self, contempt/disgust towards friend, indignation/anger towards friend, no feeling/other feeling) and rate the intensity of unpleasantness they would endure as a result of this situation using a 1-7 point Likert scale. Participants are then asked to select the action that they would most strongly feel like doing (creating distance from self, hiding, apologising, creating distance from friend, verbally or physically attacking/punishing friend or no action/other action). Based on the concept that discrete emotions evoke distinct action tendencies (Roseman et al., 1994), these action tendencies correspond to a list of moral sentiments and participants are asked to select the strongest emotion experienced. Before starting the task, participants enter their name and the name of their best friend and rate how close they feel towards their best friend.

How would you feel about this behaviour?

X is selfish towards Y

How strongly would you experience unpleasant feelings ?

1	2	3	4	5	6	7
not unpleasant						extremely unpleasant

Please select the feeling that you would experience most strongly (check only one box):

- ☐ Guilt
- ☐ Shame
- ☐ Contempt/Disgust towards self
- ☐ Contempt/Disgust towards friend
- ☐ Indignation/Anger towards friend
- ☐ No Feeling / Other Feeling

Please select the action that you would most strongly feel like doing (check only one box):

- ☐ Feel like creating distance from yourself
- ☐ Feel like hiding
- ☐ Feel like apologizing/fixing what you have done
- ☐ Feel like creating distance from your friend
- ☐ Feel like verbally or physically attacking/punishing your friend
- ☐ No Action / Other Action

This is statement Number **16** out of 36

Continue

Figure III.1: Self-agency condition of the modified version of the VMST (Zahn et al., 2015a). The participant (X) acts unpleasantly towards their best friend (Y). Participants rate the unpleasantness of the scenario, the feeling they would most strongly experience and the action they would strongly feel like doing in response to the scenario and experienced emotion.

How would you feel about this behaviour?

Y is selfish towards X

How strongly would you experience unpleasant feelings ?

1	2	3	4	5	6	7
not unpleasant						extremely unpleasant

Please select the feeling that you would experience most strongly (check only one box):

- ☐ Guilt
- ☐ Shame
- ☐ Contempt/Disgust towards self
- ☐ Contempt/Disgust towards friend
- ☐ Indignation/Anger towards friend
- ☐ No Feeling / Other Feeling

Please select the action that you would most strongly feel like doing (check only one box):

- ☐ Feel like creating distance from yourself
- ☐ Feel like hiding
- ☐ Feel like apologizing/fixing what you have done
- ☐ Feel like creating distance from your friend
- ☐ Feel like verbally or physically attacking/punishing your friend
- ☐ No Action / Other Action

This is statement Number **9** out of 36

Continue

Figure III.2: Other-agency condition of the same hypothetical scenario of the modified version of the VMST presented in Figure III.1. Now the participant's friend (Y) acts unpleasantly towards the participant (X). The same measures are collected as in the self-agency condition.

III.3.8) Experimental neuropsychological testing: Brief Implicit Association Test

The self-contempt Brief Implicit Association Test (BIAT), another experimental measure developed by our research group in collaboration with Prof Rüsç and Dr Bogenhausen, was employed as an indirect measure of self-contempt biases, evaluating the association of contempt or disgust with oneself relative to others. Further, we included an established BIAT (Sriram & Greenwald, 2009) used to assess implicit self-esteem. The rationale for the development of this computerised task was based on the endeavour to measure self-contempt biases without the participants' awareness of what the task captures. This strategy is meant to prevent distortions in the participants' response. The task design is based on a similar test, the Implicit Association Test (IAT; Greenwald, McGhee & Schwartz, 1998), which has been validated to measure implicit self-esteem (Greenwald & Farnham, 2000).

The BIAT uses complementary pairs of concepts and attributes which the participant needs to sort together. The speed in which participants respond is reflective of the strength of the association within the two pairs of categories that have to be sorted together (Greenwald & Farnham, 2000; Greenwald, McGhee, & Schwartz, 1998). Specifically, participants are instructed to decide with a response if two sets of items match an associated concept-attribute pair and are asked to give a different response should the item pairs not match (Greenwald & Farnham, 2000). Participants respond as quickly as possible by pressing left and right keys on a computer keyboard (Greenwald & Farnham, 2000). As aforementioned, the automatic association between a concept (e.g. self) and an attribute (e.g. contemptuous) is assessed by calculating differences in speed between two

conditions. In condition 1, words indicative of ‘self’, i.e. the participant, and words relating to contempt share the same response key (i.e. require the pressing of the right-side key). In condition 2, words that address the ‘self’ (i.e. the participant) and words that relate to anxiety share the same response key (here, the left key needs to be pressed). Examples of incorrect and correct answers in both conditions are given in Figure III.3 (condition 1) and Figure III.4 (condition 2).

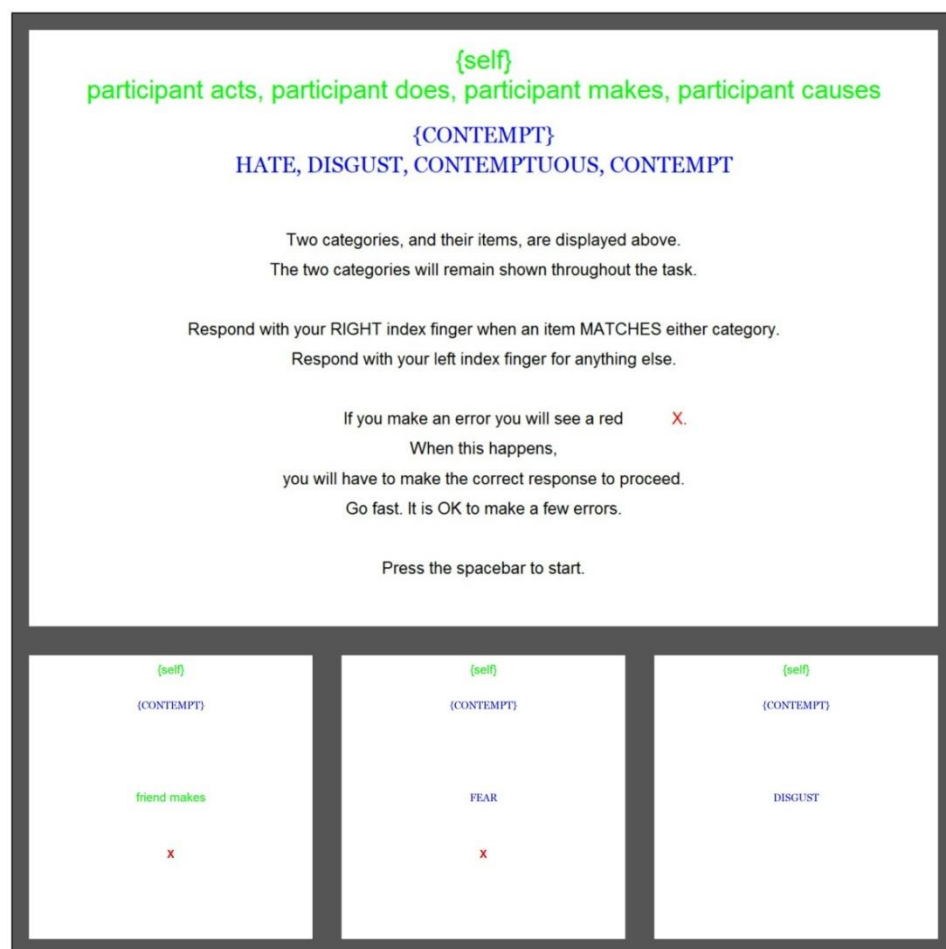


Figure III.3: Condition 1 of the BIAT implicit self-contempt task, measuring response speed and correct responses for the concept ‘self’ and contempt vs ‘other’ and contempt, alongside the non-focal category anxiety. Correct responses in this condition are words related to ‘self’ and contempt.

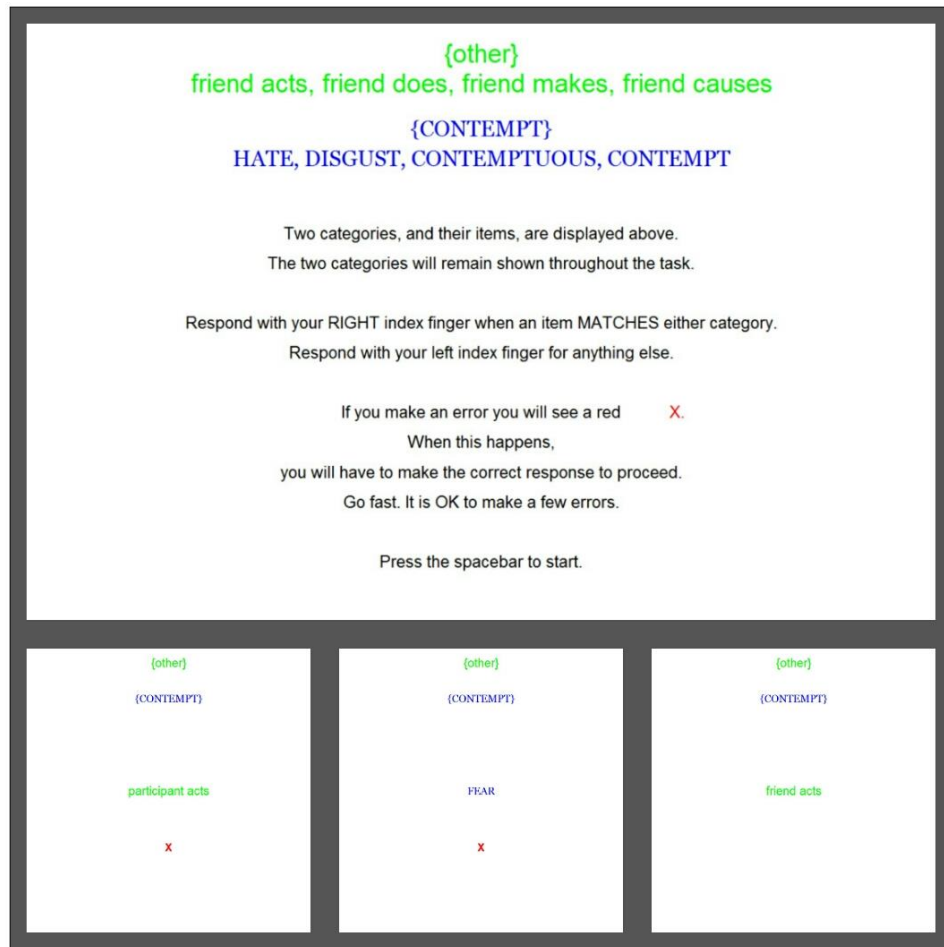


Figure III.4: Condition 2 of the BIAT implicit self-contempt task, measuring response speed and correct responses for the concepts ‘self’ and contempt versus ‘other’ and contempt, alongside the non-focal category anxiety. Correct responses in this condition are words related to ‘other’ and contempt.

The BIAT consists of two experimental tasks that assess implicit self-contempt, whereby the categories consist of self-agency, other-agency, contempt and a non-focal category which is either anxiety or anger. In the implicit self-esteem task, the categories ‘self’ and ‘other’ are attributed to ‘good’ (positive valence) and ‘bad’ (negative valence). Greenwald et al. (2002) emphasise that this task design, due to its use of complementary pairs of concepts and attributes, is limited to measuring the relative strength of pairs of associations rather than the

absolute strength of single associations. The authors conclude, however, that the task is meaningful in practice due to the opposing, yet complementary quality of many socially meaningful categories, i.e. good and bad (Greenwald et al., 2002; Greenwald & Farnham, 2000).

III.3.9) Statistical Analysis

Statistical analysis of clinical features and self-blaming emotional biases was of an explorative nature, aimed at investigating patterns of MDD patients with and without anxious distress compared to a sample of HC participants. This approach was chosen based on findings of the NeuroMooD trial that showed differences in treatment response between MDD patients of the anxious distress subtype and patients without anxious distress (see chapter II).

Data obtained through the administration of the modified VMST was exported from Excel and analysed with SPSS 24 (<https://www.ibm.com/analytics/spss-statistics-software>). Percentage values of emotions and action tendencies chosen for each social scenario were aggregated per participant in the self-agency, and other-agency conditions, mean and standard deviation were calculated for measures of unpleasantness in both conditions. Identical to analysis strategies in previous studies (Green et al., 2013, Zahn et al., 2015a), self-contempt bias was measured by subtracting percentage values of contempt/disgust towards the best friend in the other-agency condition from self-directed contempt in the self-agency condition.

BIAT data was exported from Inquisit 3 (<https://www.millisecond.com/products/Inquisit3/>) and analysed with SPSS 24 (<https://www.ibm.com/analytics/spss-statistics-software>). Scoring algorithms and

analyses strategies were based on the improved scoring algorithm created by Nosek (2005, May 27).

Trials with an error rate of higher 30% of 32 trials were excluded from the analyses; similarly, trials, where more than 10% of participant responses had a latency of less than 300 milliseconds, were excluded. Self-contempt bias was measured by subtracting the mean value of latency for the category 'self and contempt' (16 trials) minus the mean value of the latency for the category 'other and contempt' (16 trials), divided by the standard deviation of latency computed for all 32 trials. Hereby, a more positive total score is understood as being indicative of a higher degree of self-contempt. In the analysis of implicit self-esteem, the categories 'others and good' were subtracted from the 'self and good' category. Hereby, a more positive total score is meant to be reflective of a lower degree of self-esteem.

III.4) Results

III.4.1) Demographic characteristics

Table III.1: Demographic characteristics of the study groups

	MDD with anxious distress	MDD without anxious distress	HC participants
Sample size (n)	33	16	18
Sex	6 m / 27 f	3 m / 13 f	3 m / 15 f
NeuroMood part.	28	15	n/a
Not NeuroMood	5	1	n/a
NeuroMood comp.	21	14	n/a
	M; SD [Min - Max]	M; SD [Min - Max]	M; SD [Min - Max]
Age in years	37.42; 10.81 [20 - 59]	33.88; 8.25 [20 - 49]	42; 16.16 [20 - 59]
Years of education	17.06; 2.49 [11 - 22]	17.27; 3.46 [11 - 23]	16.61; 2.64 [11 - 21]

NeuroMood part. = NeuroMood participants, NeuroMood comp = NeuroMood completers, m = male, f = female; M = mean, SD = standard deviation, n/a = not applicable; [M-M] = Minimum–Maximum. Mean age all MDD: M=36.72; SD=10.10, [20–59]; Mean years of education all MDD: M=17.22; SD =2.82, [11-23]; No between-group differences in demographical characteristics, $F(4, 126)=1.15$, $p=.338$; Wilks' Lambda=.93; $\eta^2=.04$.

III.4.2) Hypothesis-driven analysis of moral sentiments on the modified VMST: indignation/anger towards others and self-blame emotional biases

A multivariate general linear model analysis was conducted, exploring moral sentiments and self-blaming emotional biases in N=65 participants, including MDD patients of the anxious distress subtype (n=31), MDD patients without anxious distress (n=16) and HC participants (n=18). Descriptive statistics of this sample are presented in Table III.2. At a multivariate level, no effect of group was detected, no differences were found between MDD groups and HC

participants in the selection of moral sentiments on the modified VMST, $F(10, 116)=.85$, $p=.586$, Wilks' Lambda=.87, $\eta^2=.07$.

Contrary to the hypothesis, levels of indignation and anger directed towards others were not found to be increased in MDD patients of the anxious distress subtype, $F(2,62)=2.06$, $p=.136$, $\eta^2=.06$, nor were differences found between MDD groups and HC participants in the tendency to show self-blaming emotional biases, such as shame ($F(2,62)=0.58$, $p=.564$, $\eta^2=.02$), guilt ($F(2,62)=0.20$, $p=.822$, $\eta^2=.01$), agency incongruent self-blame ($F(2,62)=0.93$, $p=.401$, $\eta^2=.03$) or self-contempt ($F(2,62)=0.52$, $p=.600$, $\eta^2=.02$). Self-blaming emotional biases were not found to be more pronounced in MDD without anxious distress compared to MDD with anxious distress. Equality of error variances was assumed.

Table III.2: Descriptive statistics: VMST moral sentiments

Condition and study group		M	SD	n
VMST_oa indignation/anger towards friend (pgt)	MDD anxious distress	34.23	20.94	31
	MDD non-anxious	21.88	12.08	16
	HC	31.48	23.34	18
	Total	30.43	20.25	65
VMST_sa shame (pgt)	MDD anxious distress	25.81	13.19	31
	MDD non-anxious	29.87	12.97	16
	HC	29.32	16.70	18
	Total	27.78	14.10	65
VMST_sa guilt (pgt)	MDD anxious distress	30.29	13.90	31
	MDD non-anxious	27.28	14.49	16
	HC	28.40	14.87	18
	Total	29.15	14.13	65

VMST agency incongruent self-blame	MDD anxious distress	16.31	19.19	31
	MDD non-anxious	17.71	16.63	16
	HC	10.19	16.20	18
	Total	14.96	17.78	65
VMST self-contempt bias	MDD anxious distress	6.09	17.47	31
	MDD non-anxious	4.86	16.47	16
	HC	-0.31	30.46	18
	Total	4.02	21.46	65

Agency incongruent self-blame = self-blaming emotions in the other-agency condition; M = mean, SD = standard deviation, n = sample size, VMST = value-related moral sentiment task (modified version), oa = other-agency, sa = self-agency, pct = percentage of trials where this response was selected; MDD = major depressive disorder, HC = healthy control participants

III.4.3) Explorative analysis of action tendencies on the modified VMST

A multivariate general linear model was used in the analysis of differences between groups regarding action tendencies.

In the present sample of MDD patients with anxious distress (n=31), MDD without anxious distress (n=16) and HC participants (n=18), groups did not differ at a multivariate level, $F(8,118) = 1.58$, $p = .139$, Wilks' Lambda = .82, $\eta^2 = .10$. Equality of error variances could not be assumed for the tendency to distance oneself in the other-agency condition (Levene's test, $F(2,62)$, $p = .053$). Demographics are displayed in Table III.3.

There was a trend for an interaction effect between groups and the tendency to hide from the best friend in the self-agency condition, $F(2,62) = 2.90$, $p = .062$, $\eta^2 = .09$. The tendency to hide was increased in MDD patients with anxious distress compared with HC participants, but not compared with MDD

patients without anxious distress. This trend only became significant when uncorrected for multiple comparisons $t(2)=2.41$, $SD=3.50$, $p=.019$.

Table III.3: Descriptive statistics: VMST action tendencies

Condition and study group		M	SD	n
VMST_oa attacking friend (pgt)	MDD anxious distress	9.14	12.05	31
	MDD non-anxious	3.13	6.08	16
	HC	4.01	14.49	18
	Total	6.24	11.85	65
MST_oa distance from friend (pgt)	MDD anxious distress	39.78	18.82	31
	MDD non-anxious	36.11	16.85	16
	HC	44.14	30.10	18
	Total	40.09	21.95	65
MST_sa distance from self (pgt)	MDD anxious distress	10.22	13.15	31
	MDD non-anxious	7.99	9.29	16
	HC	4.01	7.33	18
	Total	7.95	11.07	65
MST_sa hiding (pgt)	MDD anxious distress	13.98	13.06	31
	MDD non-anxious	11.11	13.15	16
	HC	5.56	7.38	18
	Total	10.94	12.15	65

M = mean, SD = standard deviation, n = sample size, VMST = value-related moral sentiment task (modified version), oa = other-agency, sa = self-agency, pgt = percentage of trials where this action tendency was selected; MDD = major depressive disorder, HC = healthy control participants

III.4.4) Investigating clinical features between groups: stressful life events

At a multivariate level, there was a significant effect of group on stressful life event measures ($F(6,80)=3.06$, $p=.009$; Wilks' Lambda=.66; $\eta^2=.19$). Analysis of each dependent variable, using a Bonferroni adjusted alpha level of .017, showed that there was no contribution of the number of stressful life events experienced in the last year as measured with the Life Events Questionnaire, $F(2,42)=1.27$, $p=.291$; $\eta^2=.06$. Equality of error variances could not be assumed, Levene's test $F(2,42)=3.44$, $p=.041$. The three study groups differed in regard to the number of stressful life events experienced more than a year ago, $F(2,42) = 5.38$, $p=.008$; $\eta^2=.20$, and in terms of the CTQ self-report measure, $F(2,42)=.24$, $p=.009$, $\eta^2=.20$. MDD patients with anxious distress experienced significantly more stressful life events more than a year ago than MDD patients without anxious distress or HC participants (Table III.4). MDD patients of the anxious distress subtype and non-anxious patients did not differ regarding their sum scores on the CTQ, yet patients with anxious distress scored significantly higher on this measure than HC participants (Table III.5).

Table III.4: Descriptive statistics: past stressful life events

Condition and study group		M	SD	n
Life Events Questionnaire Number of events In the last year	MDD anxious distress	1.15	1.07	13
	MDD non-anxious	1.36	1.34	14
	HC	0.78	0.73	18
	Total	1.07	1.05	45
Life Events Questionnaire Number of events more than a year ago	MDD anxious distress	5.31	2.90	13
	MDD non-anxious	3.00	2.48	14
	HC	2.44	2.12	18
	Total	3.44	2.71	45

Childhood Trauma Questionnaire sum score	MDD anxious distress	43.54	13.07	13
	MDD non-anxious	40.50	12.12	14
	HC	31.44	7.99	18
	Total	37.76	11.97	45

M = mean, SD = standard deviation, n = sample size, MDD = major depressive disorder, HC = healthy control participants

Table III.5: Study group comparisons: past stressful life events

Dependent variable and study groups			M Dif	SE	p	95% CI for Difference	
						LB	UB
Life Events Questionnaire Number of events in the last year	MDD	MDD	-0.20	0.40	.617	-1.02	0.61
	anxious distress	non- anxious HC	0.38	0.38	.329	-0.39	1.14
	MDD	MDD	0.20	0.40	.617	-0.61	1.02
	non- anxious	anxious distress HC	0.58	0.37	.128	-0.17	1.33
	HC	MDD	-0.38	0.38	.329	-1.14	0.39
		anxious distress MDD non- anxious	-0.58	0.37	.128	-1.33	0.17
Life Events Questionnaire Number of events more than a year ago	MDD	MDD	2.31	0.95	.020*	0.38	4.23
	anxious distress	non- anxious HC	2.86	0.90	.003*	1.05	4.68
	MDD	MDD	-2.31	0.95	.020*	-4.23	-0.38
	non- anxious	anxious distress HC	0.56	0.88	.532	-1.22	2.34
	HC	MDD	-2.86	0.90	.003*	-4.68	-1.05
		anxious distress MDD non- anxious	-0.56	0.88	.532	-2.34	1.22
Childhood Trauma Questionnaire Sum score	MDD	MDD	3.04	4.22	.476	-5.48	11.56
	anxious distress	non- anxious HC	12.09	3.99	.004*	4.05	20.14

MDD non- anxious	MDD anxious distress	-3.04	4.22	.476	-11.56	5.48
	HC	9.06	3.90	.025*	1.18	16.94
HC	MDD anxious distress	-12.09	3.99	.004*	-20.14	-4.05
	MDD non- anxious	-9.06	3.90	.025*	-16.94	-1.18

The mean difference is significant at the .05 level. Confidence intervals for mean difference are adjusted for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

M Dif = mean difference, SE = standard error of the mean, CI = confidence interval, LB = lower bound, UB = upper bound

III.4.5) Further explorative analyses of additional clinical measures

There was a significant effect of group in the multivariate GLM analysis of self-esteem and implicit self-contempt in MDD patients and HC participants, $F(8,100)=13.04$, $p<.0005$, Wilks' Lambda=0.24, $\eta^2=.51$. Furthermore, an interaction effect of study group with scores on the Rosenberg Self-Esteem Scale was found $F(2,53)=77.54$, $p<.0005$, $\eta^2=.75$, implying that MDD patients with anxious distress showed significantly lower scores, $M\ dif=-13.97$, $SE=1.21$, $p<.0005$, $CI[-16.39;-11.56]$. No significant differences in explicit self-esteem (Rosenberg Self-Esteem scale) or implicit self-esteem (BIAT) were found between MDD patient groups. MDD patients and HC participants did not differ on measures of implicit self-contempt. Group statistics are presented in Table III.6.

Table III.6: Descriptive statistics: self-esteem and implicit self-contempt measures

Condition and study group		M	SD	n
BIAT	MDD	0.34	0.37	28
contempt_anxiety_D_Score	anxious distress			

	MDD non-anxious	0.30	0.28	12
	HC	0.38	0.63	16
	Total	0.34	0.44	56
BIAT contempt_anger_D_Score	MDD anxious distress	0.03	0.38	28
	MDD non-anxious	-0.06	0.42	12
	HC	-0.05	0.40	16
	Total	-0.01	0.39	56
BIAT self_esteem_D_Score	MDD anxious distress	0.57	0.44	28
	MDD non-anxious	0.39	0.51	12
	HC	0.69	0.35	16
	Total	0.57	0.44	56
Rosenberg Self-Esteem Scale total_score	MDD anxious distress	19.96	3.27	28
	MDD non-anxious	19.33	3.52	12
	HC	33.94	4.89	16
	Total	23.82	7.48	56

M = mean, SD = standard deviation, n = sample size, MDD = major depressive disorder, HC = healthy control participants

Further explorative analyses, specific to the MDD patient groups only, compared MDD with and without anxious distress on additional clinical measures. Independent samples t-tests established significant differences between MDD patient groups on the POMS anger-hostility and POMS tension-anxiety subscales, with MDD patients of the anxious distress subtype presenting higher scores on both measures (Table III.7, Table III.8). These findings, however, were not reflected in correlation analyses of POMS scores and variables of the modified VMST (Table III.9).

MDD patient groups did not differ on other clinical measures, including BDI-II and MADRS scores, number of previous MDEs or GAF and SOFAS scores.

Table III.7: MDD group statistics: clinical measures

Clinical measure and study group		n	M	SD	SE
Baseline_BDI	MDD anxious distress	33	31.36	9.90	1.72
	MDD non-anxious	16	28.31	6.85	1.71
Baseline_MADRS	MDD anxious distress	28	24.04	6.44	1.22
	MDD non-anxious	15	20.60	7.59	1.96
Number of previous MDEs	MDD anxious distress	28	13.32	25.63	4.84
	MDD non-anxious	15	10.00	16.40	4.23
GAF_baseline	MDD anxious distress	27	54.70	6.14	1.18
	MDD non-anxious	15	56.07	6.43	1.66
SOFAS_baseline	MDD anxious distress	28	58.79	7.88	1.49
	MDD non-anxious	15	57.80	9.20	2.38
POMS Anger/Hostility Scale	MDD anxious distress	28	7.64	4.08	.77
	MDD non-anxious	15	4.67	3.94	1.02
POMS Tension/Anxiety Scale	MDD anxious distress	28	10.14	4.25	.80
	MDD non-anxious	15	5.73	3.31	.85

Insignificant results of independent t-tests of the clinical measures listed, all two-tailed: BDI-II: $t(47)=1.11$, $p=.274$, MADRS: $t(41)=1.57$, $p=.125$, Number of MDEs: $t(41)=.45$, $p=.653$, GAF: $t(40)=-.68$, $p=.509$, SOFAS: $t(41)=.37$, $p=.714$; MDEs = major depressive episodes, n = sample size, M = Mean, SD = standard deviation, SE = standard error of the mean

Table III.8: Independent samples t-test: POMS subscales

	t-test for Equality of Means						
	t	df	p	M Dif	SE Dif	95% CI of the Difference	
						Lower	Upper
POMS Anger/Hostility Scale	2.31	41	.026	2.98	1.29	0.37	5.58
POMS Tension/Anxiety Scale	3.49	41	.001	4.41	1.26	1.86	6.96

Equal variances assumed, significance level of $p \leq .05$, 2-tailed; df = degrees of freedom, M = mean, Dif = difference, SE = standard error of the mean

Table III.9: Spearman's rho correlations: action tendencies, sentiments and POMS

		VMST_oa Indignation tow. friend [pgt]	VMST_oa Attacking friend [pgt]	POMS Tension / Anxiety Scale	POMS Anger / Hostility Scale	VMST_sa Shame [pgt]	VMST_sa Hiding [pgt]
VMST_oa Indignation tow. friend [pgt]	CC	1.000	.328**	0.092	0.179	-.259*	0.179
	Sig.		0.007	0.556	0.251	0.036	0.151
	N	66	66	43	43	66	66
VMST_oa Attacking friend [pgt]	CC	.328**	1.000	0.272	.393**	-0.096	.254*
	Sig.	0.007		0.077	0.009	0.443	0.040
	N	66	66	43	43	66	66
POMS Tension / Anxiety Scale	CC	0.092	0.272	1.000	.523**	0.052	0.194
	Sig.	0.556	0.077		0.000	0.740	0.212
	N	43	43	43	43	43	43
POMS Anger / Hostility Scale	CC	0.179	.393**	.523**	1.000	-0.236	0.105
	Sig.	0.251	0.009	0.000		0.127	0.505
	N	43	43	43	43	43	43
VMST_sa Shame [pgt]	CC	-.259*	-0.096	0.052	-0.236	1.000	-0.030
	Sig.	0.036	0.443	0.740	0.127		0.810
	N	66	66	43	43	66	66
VMST_sa Hiding [pgt]	CC	0.179	.254*	0.194	0.105	-0.030	1.000
	Sig.	0.151	0.040	0.212	0.505	0.810	
	N	66	66	43	43	66	66

CC = correlation coefficient, Sig. = (2-tailed); ** Correlation is significant at the .01 level (2-tailed);

* Correlation is significant at the .05 level (2-tailed)

There was no statistically significant difference between MDD patients with and without anxious distress in the overall engagement with treatment in the NeuroMooD trial, assessed as the summed frequency in strategy use throughout the trial ($U=102.000$, $n_{\text{MDDanxious}}=21$, $n_{\text{MDDnon-anxious}}=14$, $p=.135$, two-tailed).

Finally, Pearson chi-square analyses did not show significant associations between MDD of the anxious distress subtype vs patients without anxious distress and the intake of effective dosages of antidepressant medication $\chi^2(1)=0.19$, $p=.666$. In the anxious distress group, $n=15$ patients were on a stable dose of antidepressants compared with $n=7$ MDD patients in the non-anxious group. Further, no associations were found between MDD of the anxious/non-anxious subtype and NeuroMooD withdrawal rates after randomisation, $\chi^2(1)=1.04$, $p=.307$, six MDD anxious distress patients and one non-anxious MDD patient withdrew. No associations were found between MDD anxious/non-anxious subtypes and first-degree family history of axis-I disorders, $\chi^2(1)=1.56$, $p=.211$. Twenty-one MDD patients with anxious distress presented with a family history of MDD and nine patients without anxious distress.

III.5) Discussion

III.5.1) Discussion of main findings

This chapter aimed to explore differences between MDD patients of the anxious and non-anxious subtype as classified with the anxious distress specifier of DSM-5 (APA, 2013). It was hypothesised that MDD patients with anxious distress would show increased indignation/anger towards others compared with MDD patients without anxious distress. It was further predicted that self-blaming emotional biases would be more pronounced in non-anxious MDD and that patients of the anxious distress subtype would have encountered stressful life events in higher frequency compared with non-anxious MDD patients.

The first prediction was confirmed in that MDD patients with anxious distress showed higher levels of hostility/anger on the POMS compared with both non-anxious MDD and HC groups. Contrary to our prediction, however, this increased proneness towards external anger was not found when using the modified version of the VMST, neither when examining the subjective emotional quality (anger/indignation towards others), nor the associated action tendency (attacking others). Interestingly, anxious distress subtype patients displayed higher levels of feeling like hiding when blaming themselves compared with the HC group, although this pattern did not differ significantly from the non-anxious distress patient group.

The second prediction was not confirmed as both MDD subgroups failed to show evidence of self-blaming emotional biases on the modified VMST.

The third prediction was confirmed partly by showing that anxious distress subtype patients had experienced past stressful life events more frequently than

patients without anxious distress, although patient groups did not differ on measures of early life trauma. Nevertheless, MDD patients with anxious distress were found to have experienced childhood trauma more frequently than HC participants. Anxious and non-anxious MDD patients did not differ on any other clinical measures.

The finding of increased anger/hostility on the POMS in the anxious distress MDD group is in keeping with the clinical literature but has not previously been demonstrated using a psychometric scale. Anger on the POMS was associated with attack tendencies on the modified VMST, suggesting that there is indeed an association with approach tendencies rather than withdrawal. On the other hand, hiding was found to be increased compared with HC participants, suggesting a co-existence of both withdrawal and approach-related action tendencies in patients with anxious distress. Based on these observations, increased anger in these patients could have interfered with response to the rtfMRI neurofeedback intervention in the NeuroMooD trial. It will be important to investigate the neural differences between self-blaming biases in MDD patients with low and high levels of hostility/anger.

It was surprising to see no significant differences between both MDD groups and the HC participant group on self-contempt biases and anger, despite finding abnormalities in previous studies of remitted MDD (Green et al., 2013, Zahn et al., 2015a). Considering that a shortened version of the VMST was employed in the current research (36 items), compared to a more extensive (90) item set of the original VMST, a reduction of power may account for the non-significant findings. Furthermore, previous studies consisted of greater sample

sizes ($n=55$ MDD, Green et al., 2013; $n=101$ MDD, Zahn et al., 2015a) compared with the current study. Drawing on their findings, Green et al. and Zahn et al. speculate that self-contempt biases might be particularly characteristic of melancholic MDD rather than of other subtypes (Green et al., 2013, Zahn et al., 2015a, unpublished secondary analysis). Notably, the study sample of the research presented in this chapter consisted of low numbers ($n=11$) of MDD patients of the melancholic subtype, yet this interpretation is in keeping with a trend towards higher self-contempt bias in the melancholic subtype patients in this study ($n_{\text{MDDnon-melancholic}}=32$, $n_{\text{MDDmelancholic}}=11$, $t(41)=-1.61$, $p=.115$, $M_{\text{Dif}}=-8.97$, $SE=5.53$, $CI[-20.2;2.27]$, two-tailed). Lastly, the observed high individual variability on self-contempt biases in the current study may account for the failure to detect self-contempt biases in the MDD sample, which may suggest that, instead of being a general feature of MDD, different subgroups of MDD with and without self-contempt may exist in the MDD population.

The finding of an increased prevalence of past stressful life events in the anxious distress subtype of MDD patients suggests that anger/hostility, as well as anxiety, may potentially be mediated by a traumatic response to previous stressful life events. In the current sample, however, comorbid cases of past PTSD were rare, although these patients reported their residual PTSD symptoms to be significantly enhanced during MDEs.

III.5.2) Limitations

The following potential limitations of this research need to be considered. Formulation of hypotheses and analysis strategies, comparing anxious and non-anxious MDD, was based on previous explorative analyses of the acquired

NeuroMooD data. MDD subgroups were of unequal sample sizes. Despite differentiating between MDD patients with and without anxious distress, the severity of anxious distress experienced within the anxious distress patient sample was not further assessed. Therefore, differences in anxious distress severity may have varied across patients of this MDD subtype and may account for variability within this patient group across applied measures. Analyses, including the POMS tension/anxiety subscale, were conducted only to explore differences between, but not within non-anxious and anxious MDD patient groups.

Results of the modified VMST administered in the current study might be limited in their comparability to findings obtained by use of previous, more extended versions of the task. Contrary to the previous versions, the modified VMST lacks validation, which further restricts the interpretation of the current findings. Validity ensures that the measure captures what it intends to capture in the population where it is applied, while test validation requires a performance comparison of the novel (unvalidated) instrument with a validated measure (Fitzpatrick et al., 1998). Considering that no validation data has been generated for the modified VMST prior to its implementation in this study, its suitability for measuring self-blaming biases remains uncertain. It is noteworthy that the VMST assesses interpersonal guilt only and neglects blame related to achievement-related failures. Therefore, it might be that both MDD groups did have self-blaming biases, but that they were undetected due to the nature of the experimental task. This interpretation is supported by the observation that the majority (>70%) of MDD patients did express at least moderate levels of guilt, shame or self-contempt during the initial clinical assessment, using a validated psychopathology interview (Zahn et al., 2015b).

III.5.3) Conclusion

Research on the DSM-5 anxious distress subtype of MDD is still sparse, with a complete lack of studies investigating self-blaming emotions and related concepts in the anxious distress subtype. Furthermore, at present, no rtfMRI neurofeedback study in MDD has differentiated between anxious and non-anxious subtypes or investigated neural correlates of response to rtfMRI neurofeedback treatment in the anxious distress subtype. Considering the high prevalence of the anxious distress subtype in MDD populations, more research is needed to identify and explain observed differences further and to contribute to improvements in the understanding and treatment of this particular MDD subtype.

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Chapter IV: Social agency inference in major depressive disorder

IV.1) Abstract

The interpretation of social knowledge influences how we perceive positive and negative outcomes of situations and social interactions. This information is critical for major depressive disorder (MDD) as psychological models suggest that maladaptive causal attributions for negative events contribute to an overgeneralisation of self-blame and self-criticism in MDD, which persists even during symptom remission. One poorly understood aspect of social knowledge is how we interpret social outcomes in different contexts of preceding events. At present, it remains unclear whether internally biased causal inferences for negative outcomes contribute to the experience of overgeneralised self-blame in MDD. The work presented in this chapter aimed at contributing to the investigation of neurocognitive mechanisms underpinning self-blaming emotional biases in MDD. For this purpose, a novel experimental task was developed, the social agency inference task (SAIT) and tested in MDD patients with and without anxious distress and healthy control (HC) participants.

Contrary to the non-anxious MDD group, MDD patients of the anxious distress subtype were not found to present with self-blaming biases. This finding confirms results from the previous chapter, which demonstrated that this patient group tends to externalise blame more compared with MDD patients without anxious distress. There was no evidence of overgeneralisation of preceding actions related to internalising or externalising blame in either group. Modifications to the task design may be required to transform the SAIT into a more useful measure.

IV.2) Introduction

IV.2.1) Background

Social knowledge is crucial for the interpretation of daily life events and the evaluation of our own and others' social behaviour. Because such interpretations determine how we feel about ourselves, our successes and failures as well as other people, this information is vital for our mental health. This is why it is of particular importance to understand the underlying cognitive architecture of social knowledge in MDD.

Although previous studies have investigated different characteristics of the cognitive architecture of social knowledge (Green et al., 2013b; Green, 2011; Moll, De Oliveira-Souza & Zahn, 2008; Zakrzewski, 2008), one still poorly understood aspect of social knowledge is, how we interpret social outcomes (e.g. 'I failed in the exam') in different contexts of preceding events (e.g. 'I got drunk the night before the exam' vs 'I struggled with preparing for the exam, because I had trouble understanding my textbook'). Investigating the representation of this knowledge is important in order to understand how people make inferences about the causal agency for social actions.

Causal agency for social actions has classically been investigated using the Attributional Style Questionnaire (ASQ; Peterson et al., 1982). This instrument, however, is based on fictitious social actions created by the authors of the questionnaire rather than being based on empirical evidence collected from participants. This is one of the factors that may explain the ASQ's failure to detect reproducible abnormalities of causal attribution in patients with MDD (Green et al., 2013a).

Research suggests that patients diagnosed with MDD present with an overgeneralisation of self-blame (Abramson, Seligman, & Teasdale, 1978) and self-criticism (Beck, 1967) which might contribute to the vulnerability to depressive symptoms and is persistent even during remission (Green, Moll, Deakin, Hulleman, & Zahn, 2013b). At present, it remains unclear if internally biased causal inferences for negative outcomes contribute to the experience of overgeneralised self-blame in MDD. Investigating the cognitive architecture of self-blaming emotions, however, is important for the development of better neurocognitive and psychological treatment approaches to MDD. Learning, how MDD patients process causal inferences in social scenarios compared to non-clinical individuals may provide further insights.

IV.2.2) Specific aims and hypotheses

With the purpose of contributing to the investigation of neurocognitive mechanisms underpinning self-blaming emotional biases in current and insufficiently remitted MDD, I developed a novel task: the social agency inference task (SAIT). Specifically, the SAIT seeks to determine the frequency and intensity of agency-incongruent internalisation and externalisation of blame in hypothetical social scenarios. Here, agency-incongruence means internalising blame when another person is the agent of a social scenario and externalising blame when oneself is the agent. The rationale for designing the task in this way was based on data obtained from a pre-study that I conducted in healthy control (HC) participants. Interestingly, when HC participants were asked to provide preceding events that may have caused a given negative interpersonal action, it emerged that retribution for something the harmed person in the scenario had

done before was used as the most frequent cause for the negative interpersonal action.

Justified retribution can be used to either blame oneself for something someone else has done to oneself (agency-incongruent self-blame) or to blame someone else for something one has done to them (agency-incongruent other-blame). Given the literature on self-positive biases in healthy individuals (Dunn, Dalgleish, Lawrence, & Ogilvie, 2007; Dunn, Stefanovitch, Buchan, Lawrence, & Dalgleish, 2009; Mezulis, Abramson, Hyde, & Hankin, 2004; Taylor & Brown, 1988) and blame externalisation as a defence mechanism to stabilise self-esteem (Bentall & Kaney, 2005), the overall prediction was that participants with MDD would show a bias towards internalising rather than externalising blame when compared with HC participants. In order to investigate this prediction with the SAIT, the task was administered in a sample of symptomatic MDD patients and HC participants.

The following hypotheses were postulated:

Hypothesis 1: Patients with MDD show self-blaming emotional biases on the SAIT when compared with HC participants.

Hypothesis 2: Patients with MDD show an overgeneralisation of negative preceding actions internalising blame relative to those externalising blame when compared with HC participants.

IV.3) Methods

Social inference in MDD was investigated using the SAIT, which I have developed specifically for this study and was used to explore whether changes in social agency inferences underpin self-blaming emotions in MDD. The SAIT was developed based on data obtained from a pre-study that I carried out as outlined further in this chapter. The administration of the SAIT in MDD and HC participants occurred as part of the NeuroMooD protocol (see chapter II) and received ethical approval by the NHS Health Research Authority, NRES Committee London – Camberwell St Giles (REC reference: 15/LO/0577).

IV.3.1) Development of the SAIT: conduction of a pre-study

SAIT pre-study: methods

In order to obtain data for the SAIT, an online pre-study (REC reference number LRS-14/15-1003) was conducted upon receiving ethical approval granted by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee, King's College London. This pre-study aimed at investigating how individuals represent knowledge of events and actions preceding socially relevant outcomes. Specifically, it resulted in collecting agency-incongruent preceding events that were thought to contain a causal relationship to a number of hypothetical social actions of self- and other-agency. The pre-study consisted of two complementary versions of an online questionnaire that were disseminated to self-identifying HC participants by use of the online research tool Survey Monkey.

HC participants were presented with 60 hypothetical social scenarios (30 positive and 30 negative) and asked to vividly picture themselves and their best

friend in the presented scenario. Participants were asked to provide two different examples of potential preceding events for each social scenario. Preceding events should have occurred within the past couple of weeks prior to the (hypothetical) scenario and inherit a causal influence on the situation. Similarly to the ASQ (Peterson et al., 1982), participants were then asked to rate how much they would attribute outcomes to internal or external factors. Specifically, participants were asked how much they would blame/credit themselves or others for the situation and how much they would blame/credit uncontrollable factors. Furthermore, participants were instructed to rate the pleasantness/unpleasantness of the situation, taking the provided preceding event into account, and answered how familiar they felt with the situation and the likelihood of such a situation occurring following each preceding event.

Contrary to the ASQ, which is based on fictitious social actions created by the authors of the questionnaire (Peterson et al., 1982), the stimuli (i.e. social scenarios) presented in this pre-study were based on previously collected empirical data (Zahn et al., 2007). Zahn et al. (2007) asked HC participants to provide examples of social behaviours that cause individuals to feel guilty/shameful and grateful/proud. For a detailed description of these stimuli, see also the online supplementary methods provided by Green et al. (2013a). The stimuli chosen for the SAIT pre-study were modified by making slight amendments to the wording of the original items and by converting American English into British English. Due to the change in syntax and sentence structure, the word count of the original items was altered. The terms ‘agent’ and ‘recipient’ were changed to ‘you’ and ‘your best friend’. Despite these modifications to the original items, the conceptual meaning was not changed in order to allow items to

be still attributed to formerly established classification categories of social behaviour as evocative of a particular moral emotion (guilt/shame and gratitude/pride). For a full list of the 30 negative and 30 positive items in the self-agency and other-agency condition that were included in the pre-study, please refer to Appendix B. An example of a task scenario is given in Figure IV.1 and Figure IV.2. Before proceeding with the actual questionnaire, the following instructions were given, followed by two example runs before participants accessed the actual task:


‘Please complete all tasks, as this will help us to gain more information about how people evaluate their own and others' social behaviour, and how they interpret social outcomes in different contexts of preceding events.

We will present you with different statements describing particular imaginary scenarios, involving you and your ‘best’ friend. For these tasks, please think about the closest of your friends who fits the following requirements: your best friend should be the same gender as you. Your friend should not be related to you either genetically or by marriage. She/he should be around the same age as you (± 5 years), and the two of you should have comparable educational levels. You should not have a sexual relationship with her/him.

Please try to vividly picture yourself and your best friend in the presented fictional situations. Even if you do not think that some of the behaviours are characteristic of either you or your best friend, please try to imagine acting in the described way.

For each scenario, you will be asked to give two different examples of a preceding event or action that might have led to the described situation.

We will then ask you to rate how much you would blame/praise yourself or others for the situation, and how much you would blame/credit uncontrollable external factors. (...).'



The cognitive architecture of blame biases - Version A

Situation: In a meeting, your best friend takes all the credit for your effort.

Imagine the following situation:

In a meeting, your best friend takes all the credit for your effort.

* 281. Please give an example of a preceding event occurring within the past couple of weeks prior to the described situation:

* 282. Please rate how much you would blame yourself for this situation:

1/not at all	2	3	4	5	6	7/very much
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 283. Please rate how much you would blame others for this situation:

1/not at all	2	3	4	5	6	7/very much
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 284. Please rate how much you would blame uncontrollable external factors for this situation:

1/not at all	2	3	4	5	6	7/very much
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 285. Please rate how pleasant/unpleasant you would find this situation:

-4/very unpleasant	-3	-2	-1	0	1	2	3	4/very pleasant
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 286. Please rate how familiar you are with this situation:

1/not at all	2	3	4	5	6	7/very familiar
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

49

Figure IV.1: Display of the online answer sheet 1 (of 2) for an item presented in the SAIT pre-study. Participants were asked to provide two distinct preceding events for each social scenario followed by questions about how much they would blame themselves, others, or external factors for the situation.

* 287. Please rate how likely the situation is, given this preceding event: (0-100%):

* 288. Please give a second (different) example of a preceding event occurring within the past couple of weeks prior to the described situation:

* 289. Please rate how much you would blame yourself for this situation:

1/not at all	2	3	4	5	6	7/very much
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 290. Please rate how much you would blame others for this situation:

1/not at all	2	3	4	5	6	7/very much
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 291. Please rate how much you would blame uncontrollable external factors for this situation:

1/not at all	2	3	4	5	6	7/very much
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 292. Please rate how pleasant/unpleasant you would find this situation:

-4/very unpleasant	-3	-2	-1	0	1	2	3	4/very pleasant
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 293. Please rate how familiar you are with this situation:

1/not at all	2	3	4	5	6	7/very familiar
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 294. Please rate how likely the situation is, given this preceding event: (0-100%):

50

Figure IV.2 Display of the online answer sheet 2 (of 2) for an item presented in the SAIT pre-study. Participants were asked to provide two distinct preceding events for each social scenario followed by questions about how much they would blame themselves, others, or external factors for the situation.

SAIT pre-study: participants

Participants were recruited through the use of online adverts and university mailing lists. The adverts included the study's inclusion and exclusion criteria and contained the study link. Following the link, individuals were forwarded to the study's participant information sheet which occurred as a landing page on the study-specific Survey Monkey website.

Participants were eligible to participate if they were native in English language and of 18 years or older with no history of current psychiatric or neurological disorders, including substance or alcohol abuse. They were asked to confirm their eligibility and give online consent before proceeding with their participation. Participants were given the opportunity to answer either version (A or B) or to complete both versions of the online task.

Participants had the option to remain anonymous, but if they opted to provide their email address at the end of the questionnaire, they were reimbursed for the time taken with a £10 gift voucher. Participants email addresses were only stored until confirmation was received that the online gift voucher was redeemed. Until then, the participants' email address was stored separately from the research data.

SAIT pre-study: responses

In total, n=94 participants responded to version A of the online pre-study questionnaire, n=84 responders accessed version B of the study. Ultimately, only responses of n=19 version A participants and n=38 version B participants were considered meaningful and further regarded for the development of the SAIT. Participants who only completed the practice task of the questionnaires or

participants who mainly provided meaningless responses, e.g. single words, personal comments, letters or numbers instead of examples of preceding events were excluded. The high number of meaningless responses stopped once a note was added to the instructions, stressing that reimbursement would only be made available if meaningful responses were provided.

IV.3.2) Development of the SAIT: SAIT task design

Based on data obtained from the pre-study, the SAIT was designed to investigate whether changes in the perception of social agency inference contribute to self-blaming biases in MDD. So far, measures such as the ASQ (Peterson et al., 1982) which is based on fictitious social actions have failed to detect reproducible abnormalities of causal attributions in patients with MDD (Green et al., 2013a). Notably however, Alloy et al. (2000) used a composite of a modified version of the ASQ, the Cognitive Style Questionnaire (CSQ) and a modified version of the Dysfunctional Attitudes Scale (DAS; Weissman & Beck, 1978) to distinguish between high and low cognitive vulnerability for depression in initially non-depressed individuals. The CSQ assesses the attributional dimensions of internality, stability and globality alongside measuring participant's styles for inferring causes, consequences and self-characteristics following the occurrence of positive and negative events (Alloy et al., 2000). The authors found high cognitive risk for depression, based on the CTQ and modified DAS, to be associated with a higher lifetime prevalence of MDD compared with low cognitive vulnerability for depression (Alloy et al., 2000).

However, similar to the ASQ, the CSQ is also using fictitious social actions. The SAIT was developed as the first instrument to investigate the

influence of causal agency for social actions based on empirical evidence collected from participants.

The SAIT measures the frequency and intensity of self-directed (internalised) and externalised blame directed towards others in hypothetical social scenarios occurring between the participant and their best friend. These social situations are negative and manipulated in the attribution of causal agency (e.g.: ‘In a meeting, you take credit for your best friend’s effort’ / ‘In a meeting, your best friend takes credit for your effort.’).

For each scenario, 15 events are presented that may have preceded and led to the social situation. These 15 events were kept the same for all social scenarios and based on the data collected in the pre-study. SAIT participants are asked to choose the preceding event(s) that are most likely to have contributed to the situation.

The following instructions are given before starting the task:

‘Please imagine the situation described below and then choose the preceding event(s) which would most likely have led to this situation. Please only check more than one preceding event, if you find several preceding events equally likely. In this case, please check all of the ones which equally apply. Even if you think none of the listed preceding events is very likely, please try to find at least one preceding event that could have occurred prior to the described situation.’

Before proceeding to the next task item, participants are asked to rate how much they blame themselves and how much they blame their best friend for the

social situation on a 7-point Likert scale. Figure IV.3 and Figure IV.4 present an example of the same task item in the self-agency (participant) and other-agency (participant's best friend) condition. The SAIT consists of 15 items presented in the self-agency and other-agency condition, ultimately constituting a total of 30 social scenarios presented.

Figure IV.3: Self-agency item of the SAIT: The participant (X) takes credit for their best friend's (Y) effort. All preceding events that could have led to the presented negative social situation depict the participant's best friend (Y) as the agent.

Figure IV.4: Other-agency item of the SAIT: The participant's best friend (Y) takes credit for the participant's (X) effort. All preceding events that could have led to the presented negative social situation depict the participant (X) as the agent.

Although the pre-study provided data not only for negative items/social situations, causing guilt or shame, but also for positive social situations evoking feelings of gratitude and pride, only negative items were considered for the development of the SAIT. This decision was based on the focus of the research question (blame), alongside with practical considerations such as the number of overall items and task duration. Overall completion time for the SAIT was planned to not exceed 20–30 minutes. It took most MDD patients, however, considerably longer to complete the task compared with HC participants.

IV.3.3) Statistical analysis of the SAIT

Statistical analyses of SAIT data compared MDD patients with and without anxious distress and HC participants. The change in analysis strategy which originally aimed at comparing MDD and HC participants without

distinguishing between MDD subtypes was based on the results of the explorative analyses of the NeuroMood data which highlighted potential differences between MDD patients of the anxious and the non-anxious subtype (see chapter III). Moreover, the SAIT was analysed in the MDD completers of the NeuroMood study to investigate differences in task results pre-treatment versus post-treatment.

Self-blaming emotional biases on the SAIT were analysed by measuring means of self-blaming and other-blaming ratings on 7-point Likert scales in the self-agency and other-agency condition for each participant and across study groups. A repeated measures ANOVA was used to probe the effects of group and agency as well as their interaction.

The SAIT conceptualises overgeneralisation of agency-incongruent internalised blame relative to externalised blame as an increased number of negative internalising preceding events chosen in the other-agency condition relative to the sum of preceding externalising events chosen in the self-agency condition. A repeated measures ANOVA was conducted to investigate differences between MDD groups with and without anxious distress and HC participants.

Furthermore, a repeated measure ANOVA was used to test changes on the SAIT in the treatment groups of the NeuroMood study completers, comparing task results at baseline and after completing the NeuroMood study.

Lastly, an explorative hierarchical cluster analysis was conducted to develop a better understanding of the structure of the data.

IV.4) Results

IV.4.1) SAIT results: self-blaming emotional biases

Data was analysed for self-blaming emotions relative to blaming one's best friend (other-blame) in the self-agency condition and other-agency condition of social scenarios presented in the SAIT. Results were compared by study groups (MDD with anxious distress vs MDD without anxious distress vs HC participants). Difference scores were computed for each individual using the means of the self-blame and other-blame ratings across the 15 trials in each condition (self- and other-agency) (Table IV.1).

Table IV.1: Self-blame relative to other-blame across groups

Condition	Study Group	Mean	SD	n
Self-agency: Mean of self-blame relative to other-blame	MDD anxious distress	.56	1.57	32
	MDD non-anxious	1.25	1.86	16
	HC participants	-.18	1.36	18
	Total	.52	1.65	66
Other-agency: Mean of self-blame relative to other-blame	MDD anxious distress	.55	1.66	32
	MDD non-anxious	.21	1.70	16
	HC	1.07	.88	18
	Total	.61	1.51	66

No statistically significant effect of group ($F(2,63)=.26$, $p=.772$, $\eta^2=.008$) or agency ($F(1,63)=.07$, $p=.793$, $\eta^2=.001$) were found using a repeated measures ANOVA. An interaction effect was detected between agency and group ($F(2,63)=5.22$, $p=.008$, $\eta^2=.0142$). Self-blaming biases were found only for the non-anxious MDD group in the self-agency condition (see Figure IV.5), HC participants and MDD patients with anxious distress did not present with self-blaming biases. SD = standard deviation; n = sample size.

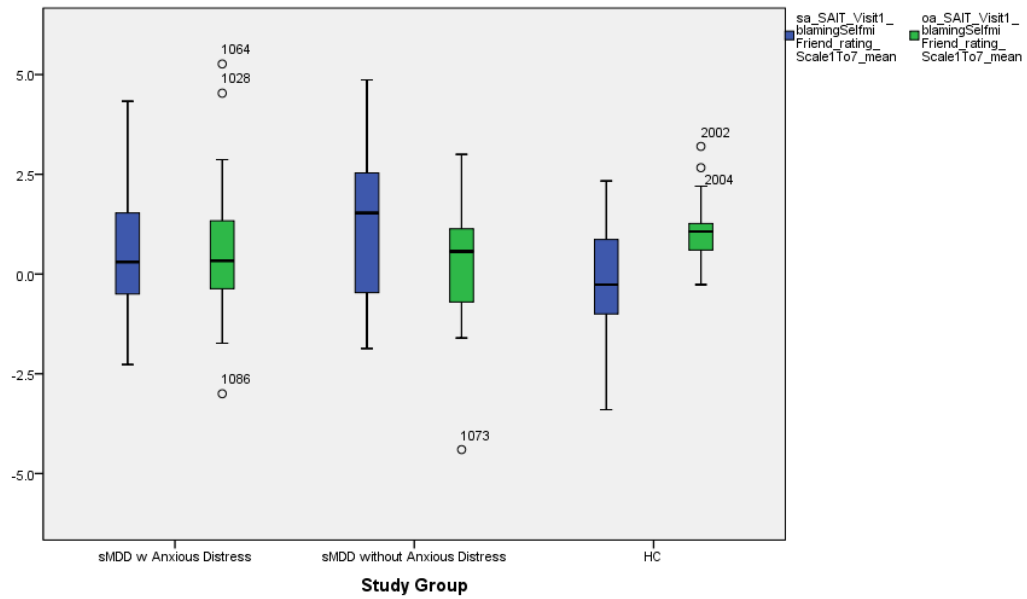


Figure IV.5: MDD patients without anxious distress show self-blaming biases in the self-agency condition ($SE=.59$, $t=2.60$, $p=.011$). MDD patients of the anxious distress subtype and HC participants do not present with self-blaming biases in the self-agency or other-agency condition. sMDD = symptomatic MDD, sa = self-agency, oa = other-agency.

IV.4.2) SAIT results: overgeneralisation of preceding event information

The sum of preceding events chosen in the self- and other-agency condition was calculated as an indicator of overgeneralised blame. Means for the sum values were calculated per group (MDD with anxious distress vs MDD without anxious distress vs HC participants) as displayed in Table IV.2. The SAIT requires participants to choose at least one preceding event per scenario and only more than one if other preceding events are perceived as equally likely. A sum value of 15 preceding events constitutes the minimum, a total of 225 events the maximum sum value per condition.

Table IV.2: Sum of preceding events chosen

Condition	Study Group	Mean	SD	n
Self-agency:	MDD anxious distress	22.13	10.25	32
	MDD non-anxious	18.19	6.56	16
	HC participants	22.67	11.89	18
	Total	21.32	10.01	66
Other-agency:	MDD anxious distress	24.06	15.42	32
	MDD non-anxious	17.94	6.93	16
	HC	23.50	13.10	18
	Total	22.42	13.27	66

The SAIT measures overgeneralisation of internalised blame relative to externalised blame as an increased number of preceding internalising blame events chosen in the other-agency condition relative to the number of preceding externalising blame events chosen in the self-agency condition. Contrary to the hypothesis, a repeated measures ANOVA did not reveal differences between groups in the number of preceding events chosen ($F(2,63)=1.21$, $p=.306$, $\eta^2=.037$) and no effect of agency was detected ($F(1,63)=1.03$, $p=.314$, $\eta^2=.016$). Moreover, no interaction effect of group and agency was observed $F(2,63)=.64$, $p=.531$, $\eta^2=.020$.

IV.4.3) SAIT results: NeuroMooD MDD group pre- vs post-treatment

Because there were no baseline abnormalities on the number of preceding events chosen on the SAIT in MDD patients, I focused the longitudinal data analysis on the self-blaming emotional bias detected in the self-agency condition at baseline in MDD patients without anxious distress. Testing whether changes in self-blaming emotional biases occurred on the SAIT in MDD completers of the treatment groups of the NeuroMooD study, task results at baseline (visit 1) were compared with results post-treatment (visit 5) in the psychological intervention and the rtfMRI neurofeedback group (see Table IV.3).

Table IV.3: Difference scores for self-blame relative to other-blame ratings pre- vs post-treatment in NeuroMood MDD patients

Condition	Treatment	MDD	Mean	SD	n
Visit1	NFB	MDD non-anxious	2.41	1.71	6
Self-agency	Psych	MDD non-anxious	0.68	1.81	8
	Total	MDD non-anxious	1.42	1.92	14
Visit5	NFB	MDD non-anxious	2.20	1.32	6
Self-agency	Psych	MDD non-anxious	0.50	2.23	8
	Total	MDD non-anxious	1.23	2.03	14

Analyses were run only in MDD patients without anxious distress in both treatment groups and only for the self-agency condition of the SAIT, as it was only MDD patients without anxious distress that showed self-blaming biases and those were restricted to the self-agency condition of the SAIT (see section IV.4.1). No change in self-blaming bias occurred post-treatment compared with baseline in the non-anxious MDD group as no effect of time was found, using a repeated measures ANOVA ($F(1,12)=.24$, $p=.633$, $\eta^2=.020$). There was no significant effect of treatment group with only a trend-wise difference ($F(1,12)=3.55$, $p=.084$, $\eta^2=.023$) and no interaction effect between time and treatment group ($F(1,12)=.00$, $p=.964$, $\eta^2=.000$).

IV.4.4) SAIT results: explorative analysis of response structure

A hierarchical cluster analysis was performed to explore further the structure of responses given by all participants ($n=66$; MDD patients with anxious distress: $n=32$, MDD without anxious distress: $n=16$, HC participants: $n=18$). Based on the dendrogram in Figure IV.6, it appears that participants gave meaningful responses and did not choose preceding events randomly. Participants showed preferences for certain preceding events in a meaningful way as preceding events of similar meaning are located in close proximity to each other in the dendrogram, displaying high levels of co-occurrence across participant responses.

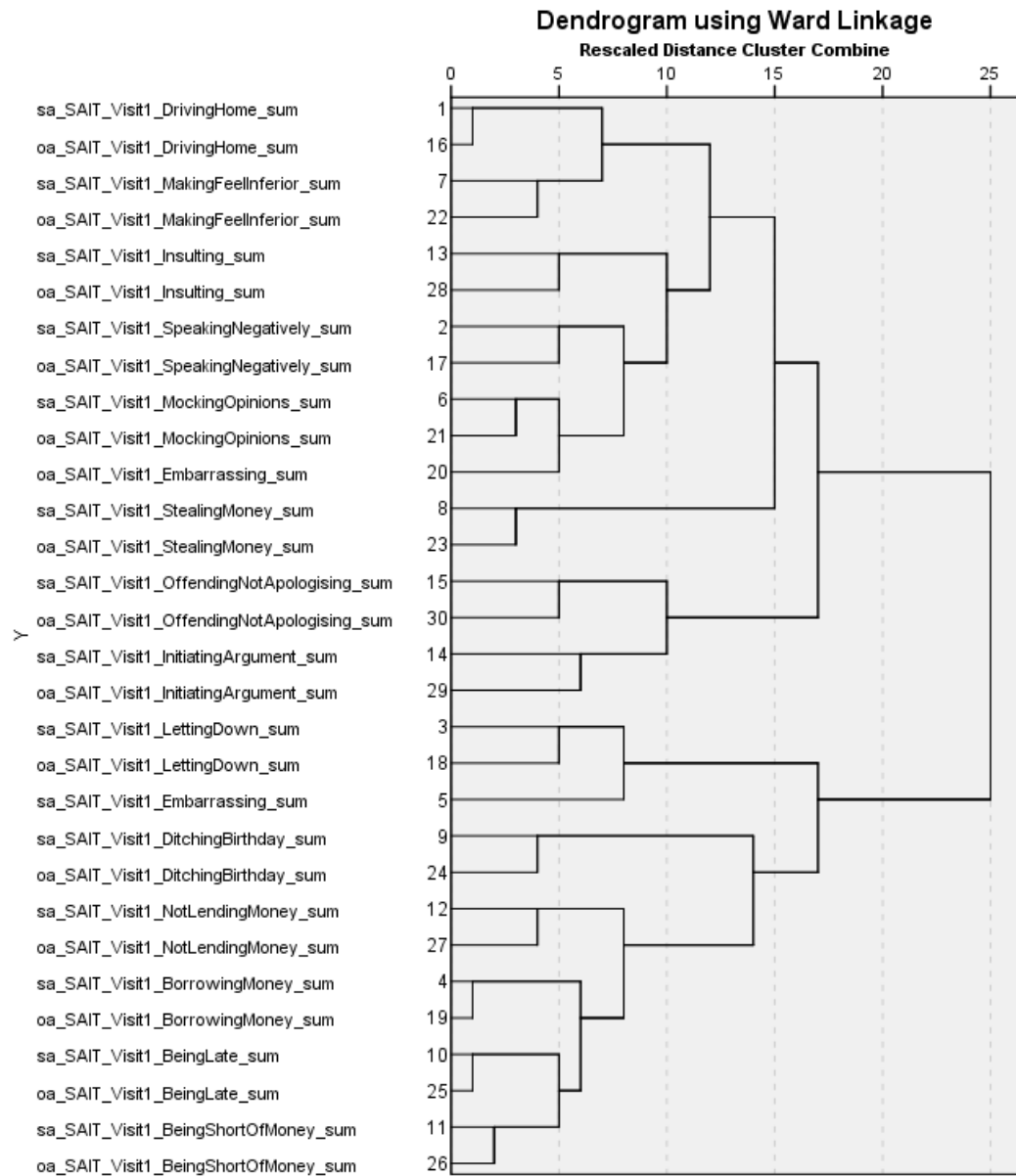


Figure IV.6: Dendrogram displaying proximity-based co-occurrence of chosen responses across participants.

IV.5) Discussion

IV.5.1) Discussion of main findings

This research aimed to test the hypotheses that patients with MDD would firstly show self-blaming emotional biases on the SAIT and secondly present with an overgeneralisation in their perception of preceding events when internalising rather than externalising blame. The results confirmed the first hypothesis in MDD patients without anxious distress who showed self-blaming emotional bias, which was found in the self-agency condition as one would expect. This self-blaming emotional bias did not change after the intervention, and there was no significant difference between intervention groups. These results differed from MDD patients with anxious distress and HC participants who showed no self-blaming emotional biases on the SAIT. There was no support for the second hypothesis in that there was no evidence of overgeneralisation of preceding actions related to internalising or externalising blame in either group.

The finding that MDD patients without anxious distress showed self-blaming emotional biases compared to the other groups confirms the results of the previous chapter in which patients with anxious distress were shown to externalise blame more than the non-anxious distress group. These findings are in keeping with the known association between anxiety and reactive anger and externalisation of blame, clinically acknowledged in that irritability is a DSM diagnostic criterion for generalised anxiety disorder (GAD) and post-traumatic stress disorder (PTSD).

Finding evidence of self-blaming biases in the self-agency condition rather than other-agency condition was expected, given that the self-agency condition

was designed to elicit self-blame and the other-agency condition was designed to elicit blaming one's best friend as described in previous papers probing moral sentiments (Zahn et al., 2009). Finding no change in self-blaming emotional biases, on the other hand, might be the result of a very low sample size in the different subgroups that were modelled (type of intervention).

Failing to find evidence for overgeneralisation of preceding events in MDD when internalising or externalising blame, could be explained by the task not being able to measure the intended function or an indicator that patients with MDD show intact inferences regarding preceding events with no overgeneralisation of those related to internalising blame. Arguments for the task not being a valid measure of overgeneralisation are overall low numbers of preceding events chosen which could be due to the task not offering enough events that were perceived as potentially relevant to the presented social situations. Contrary to the aim of the online pre-study, the data collected may not have resulted in preceding events with a close causal relationship to the social situation and instead related to tit-for-tat representations of moral indebtedness. Moreover, concluding from participants' qualitative feedback after completing the SAIT, it was challenging for them to envision the presented social scenarios as it felt difficult for them to imagine their best friend would act in such negative ways towards them. Arguments against the task being invalid are that the cluster analysis shows meaningful associations between chosen preceding events, indicating that participants made meaningful choices rather than giving responses at random. If one assumes that the task did capture differentiation/overgeneralisation of preceding social actions/events, then one would have to conclude the remarkable intactness of this complex cognitive

system in patients with MDD. Following this argument, observed self-blaming biases in MDD could then not be explained on the basis of difficulties in differentiated inferences regarding preceding events.

IV.5.2) Limitations

The following limitations need to be considered. Analogous to the modified version of the VMST, the SAIT lacks test validation, which impacts on the interpretability of the collected data. Given that participants reported challenges in relation to the stimuli/social scenarios presented in the SAIT, it is likely that this affected participants' responses. The SAIT may have failed to offer relevant preceding events with a close causal relationship to the scenarios, which could have contributed to the failure in finding evidence for an overgeneralisation of negative preceding actions internalising or externalising blame. Further, it might be disadvantageous that the task implicates the participant's best friend, as participants perceived it as difficult to imagine their best friend acting negatively towards them. This suggests that a task design which targets an unspecified or even disliked person might be preferable and would make it easier for participants to relate and hence, complete the SAIT.

IV.5.3) Conclusion

MDD patients with anxious distress did not show self-blaming emotional biases on the SAIT. This confirms results from the previous chapter, which demonstrated that this patient group tends to externalise blame more compared with MDD patients without anxious distress. Modifications of the task may turn the SAIT into a more useful measure. Changes in the design of the task could

contribute to creating a greater overlap in applicability between preceding events for a given social scenario, thereby allowing participants to overgeneralise more easily. In addition, it might be useful to gather further normative data to establish a greater pool of preceding events with a closer causal relationship to the situation. Given that it was difficult for participants to imagine that their best friend could act negatively towards them, one could consider choosing an unspecified person or a disliked, but well-known person in the other-agency condition rather than the best friend.

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Chapter V: General discussion

V.1) Introduction

V.1.1) Theoretical foundation and relevance of this research

The work presented within this thesis builds on research in support of the revised learned helplessness model as postulated by Abramson, Seligman & Teasdale (1978). This attributional model of major depressive disorder (MDD) claims that a particular dysfunctional attributional style predisposes individuals to depression. Specifically, it posits that attributing blame for negative life events in an overgeneralised and persistent manner, such that the individual automatically, yet falsely assumes themselves as being responsible for negative outcomes, increases the risk for depression. Such beliefs may develop particularly when the individual is confronted with negative life events beyond their control.

The revised learned helplessness model stresses the profound impact of self-blaming tendencies as a consequence of this maladaptive attributional style, which corresponds to overgeneralised and persistent feelings of guilt and leads to low levels of self-esteem as a further important characteristic of MDD. For example, the situation may occur that an individual fails in an exam after not having had access to the learning material required to prepare for the test adequately. A maladaptive internal, stable and global attribution style may cause the individual to conclude: 'I fail at everything. I am stupid. There is nothing I can do that would help me pass an exam.' Such thought processes omit the belief of being able to achieve better outcomes in the future. According to the revised learned helplessness model, the expectation of uncontrollability in future

situations is considered to generate many of the symptoms observed in depression, including low mood, also anxiety, dysregulation of appetite, low activity and drive, and cognitive deficits. Moreover, it is thought to contribute to changes in neurochemistry that might increase the susceptibility to MDD (Hoffman et Al'Absi, 1998).

Considerable research has been established in support of the revised learned helplessness model, highlighting the depressogenic characteristic of overgeneralised self-blaming biases in MDD compared to a diminished tendency to experience other-blaming emotions, i.e. indignation/anger towards others (Green, Moll, Deakin, Hulleman, & Zahn, 2013; Zahn et al., 2015). The neural basis of self-blaming biases in MDD has been established in medication-free remitted MDD and found to be involving abnormal connectivity patterns between the right superior anterior temporal lobe (rSATL) and the subgenual cingulate cortex. Hyper-connectivity between the rSATL and the posterior subgenual cortex (SC) was associated with recurrence in remitted MDD within 14 months (Lythe et al., 2015). These findings built the foundation for the work presented in this thesis, as they inspired the investigation of self-blaming biases by means of a newly designed experimental task, the social agency inference task (SAIT) and the testing of the clinical benefits of a novel treatment protocol. A self-guided psychological intervention was employed, with and without real-time fMRI (rtfMRI) neurofeedback, aimed at tackling the neurocognitive architecture of self-blaming emotional biases in MDD. The development of novel treatment approaches is needed as a high number of MDD patients do not fully respond to standard forms of treatment and present with a recurrent course of illness with multiple major depressive episodes (MDEs) or a chronic persistence of symptoms.

This is particularly the case for the anxious distress subtype of MDD, which seems to vary from non-anxious MDD in certain clinical characteristics, often showing a poor response to treatment (Gaspersz et al., 2017). In current clinical practice, complex interventions such as cognitive behavioural therapy (CBT) do not target self-blaming biases in MDD specifically. Compassion-focused therapy (CFT) comes closest to this aim by facilitating that patients tackle their maladaptive self-criticism with self-kindness. Cognitive therapy addresses dysfunctional beliefs more broadly, using Socratic dialogue.

The research presented in this thesis aimed at investigating the neurocognitive basis of self-blaming emotional biases in MDD, while addressing the need for new intervention approaches for early treatment-resistant MDD.

V.1.2) Hypotheses, findings and limitations of this work

In chapter II, using a randomised controlled trial in MDD patients with early treatment-resistance (NeuroMooD), I investigated whether guilt-rtfMRI neurofeedback is superior over a psychological intervention in reducing depressive symptoms and self-blame while increasing self-esteem. The study further investigated whether the rtfMRI neurofeedback group was able to decrease self-blame-selective hyper-connectivity between the posterior SC and the right rSATL. Further, the study hypothesised that improvements in symptoms should be associated with decreases in self-blame-selective hyper-connectivity in the rtfMRI neurofeedback group.

Both interventions were demonstrated to be safe for MDD patients and found to improve depression scores by 46%, with response rates of more than 55% in both treatment groups. These findings are in line with previously

published studies that established clinical benefits of rtfMRI neurofeedback interventions in MDD (Linden et al., 2012; Mehler et al., 2018; Young et al., 2017; Young et al., 2014). Contrary to the hypothesis, however, rtfMRI neurofeedback was not found to be superior in reducing depression scores compared with the psychological intervention group. Nevertheless, as predicted, rtfMRI neurofeedback training resulted in a reduction in functional connectivity between the posterior SC and the rSATL for guilt relative to indignation. This change in connectivity was, however, not associated with the reduction in depressive symptoms within the rtfMRI neurofeedback group.

Although no intervention group differences could be demonstrated on primary and secondary outcome measures, it is unlikely that the improvement in depressive symptoms solely occurred as the consequence of spontaneous remission or due to placebo-like effects. Placebo-response rates are generally estimated to be approximately 30% (Walsh, Seidman, Sysko, & Gould, 2002), well below the >55% observed in this study. Further, inclusion was restricted to early treatment-resistant, and recurrent MDD patients were included with stable symptoms, which further minimises the likelihood of symptom changes occurring due to spontaneous remission.

Similar to this study, also Mehler et al. (2018) found no group differences between the active rtfMRI neurofeedback group and the rtfMRI control group in the reduction of depression scores, yet clinical improvement correlated with increased self-efficacy. The authors interpreted this as an indicator that perceived success in modifying the rtfMRI signal might have served a therapeutic role in both rtfMRI neurofeedback groups. In the NeuroMood study, benefits were associated with patients' engagement in treatment as the summed frequency of the

use of psychological strategies throughout the trial correlated with an increase in self-esteem. Improved self-esteem, in turn, was found to be associated with a reduction in depression scores in both groups. This again shows that placebo-like or spontaneous remission effects are unlikely the sole explanation for improvements of patients after the NeuroMooD interventions.

The lack of correlation between functional connectivity changes and improvement in depressive symptomatology in the rtfMRI neurofeedback group might have been the result of a limited treatment response of MDD patients of the anxious distress subtype who constituted the majority patients in the rtfMRI neurofeedback group (n=13 anxious vs n=6 non-anxious MDD). Interestingly, MDD patients with anxious distress were found to benefit significantly less from the rtfMRI neurofeedback training compared with non-anxious MDD, only 46.14% of anxious distress MDD patients halved their depression scores post-treatment, compared to a treatment response in 83.33% of patients without anxious distress. These results suggest that rtfMRI neurofeedback may show superiority over the solely psychological intervention in non-anxious MDD patients, whereas MDD patients with anxious distress show a strong response to the psychological treatment: 75% responders of the anxious distress subtype vs only 37.5% of non-anxious MDD halving their depression scores in this treatment arm. Further, these results indicate that the self-blame-selective rSATL-posterior SC neurofeedback target might be irrelevant for MDD of the anxious distress subtype, a hypothesis which requires further investigations of neural differences between MDD patients with and without anxious distress.

Various potential limitations are important in the interpretation of the presented findings, as differences between the rtfMRI neurofeedback and the

psychological intervention group might have been missed due to inadequate power. However, the effect sizes for non-superiority of the rtfMRI neurofeedback group were so small that it is unlikely that clinically relevant group differences would have been detectable in a larger sample. Moreover, the sample size was comparable to other studies that showed significant superiority of the active rtfMRI neurofeedback condition (Young et al., 2017). Effect size estimates, however, need to be interpreted with caution when derived from small samples, because of imprecise estimates of variance.

Contrary to other studies (Young et al., 2017, Young et al., 2014), the majority of patients in the rtfMRI intervention group was taking antidepressant medication which might have influenced patients' performance during the rtfMRI neurofeedback training and affected patient selection. However, this design is more in keeping with the clinical need of interventions in treatment-resistant patients, and this approach has also been taken in rtfMRI neurofeedback studies by Linden et al. and Mehler et al. (Linden et al., 2012; Mehler et al., 2018).

Contrary to other randomised rtfMRI neurofeedback trials in MDD (Mehler et al., 2018, Young et al., 2017), the NeuroMooD study was limited by lacking a rtfMRI neurofeedback control arm. As mentioned above, Mehler et al. (2018) did not find a significant difference between groups, while Young et al. (2017) demonstrated a symptom reduction of more than 50% in the active rtfMRI neurofeedback group targeting amygdala upregulation compared to only 8% improvement in the control group. It is noteworthy, however, that the control condition in Young et al.'s study did not target brain areas involved in emotion processing, which might have interfered with potentially positive psychological effects of their control intervention.

Importantly, the heterogeneity of patients in the NeuroMooD trial might have impacted on the presented findings, as MDD patients with anxious distress were predominant in number over only a few non-anxious MDD patients. Furthermore, comorbidities of past anxiety or trauma-related disorders were included with MDD patients experiencing enhanced residual symptoms during MDEs.

In chapter III, this thesis referred back to the findings of the previous chapter and explored differences between anxious and non-anxious MDD subtypes to understand their differential response to the interventions in the NeuroMooD trial. I hypothesised that MDD with anxious distress is associated with higher levels of stressful life events and anger towards others and that this leads to reduced self-blaming emotional biases as measured on the experimental tasks.

The predictions were confirmed partly, in that MDD patients with anxious distress showed elevated levels of anger and hostility on some (i.e. POMS subscale), but not all measures (modified VMST) compared with non-anxious MDD patients and HC participants. Also, the anxious MDD subtype did not differ on measures of early life trauma compared with non-anxious MDD but was found to have experienced past stressful life events more frequently. MDD groups did not differ on any other clinical measures. Notably, anxious and non-anxious MDD failed to show self-blaming biases on the modified VMST, which was a striking finding considering that more than 70% of MDD patients, when clinically assessed, expressed moderate to severe levels of guilt, shame, or self-directed contempt/disgust.

The finding of increased anger/hostility on the POMS in the anxious distress MDD group is in keeping with clinical observations of anger-related symptoms in anxiety disorders, e.g. irritability in generalised anxiety disorder (GAD). The association between anger and attack tendencies on the modified VMST are particularly interesting in the context of additional increases in hiding tendencies of the anxious MDD group compared with HC participants and suggests a co-existence of both withdrawal and approach-related action tendencies in MDD with anxious distress. The increased anger in these patients could have reduced their self-blaming biases in interpersonal contexts and thereby explain their limited response to the self-blaming bias focussed rtfMRI neurofeedback intervention in the NeuroMood trial. It will be important to investigate the neural differences between self-blaming biases in MDD patients with low and high levels of hostility/anger and anxiety. Considering the involvement of amygdala in fear and anxiety and that MDD rtfMRI interventions that target amygdala response in MDD with moderate anxiety levels have been demonstrated to be effective (Young et al., 2017, Young et al., 2014), one could speculate that amygdala-focussed rtfMRI neurofeedback might be particularly useful for the anxious subtype of depression. This is supported by studies showing positive effects of amygdala rtfMRI in disorders with significant anxiety features, such as post-traumatic stress disorder (PTSD) (Nicholson et al., 2017; Zotev et al., 2018). There is evidence that stressful early life events cause reduced positive memory bias in remitted MDD later in life, which further supports the application of amygdala-enhancing rtfMRI paradigm neurofeedback for positive autobiographical memories (Young et al., 2017; Young et al., 2014).

Failing to find differences between both symptomatic MDD groups and the HC participants in self-contempt biases or levels of indignation towards others on the modified VMST is in contrast to the existing literature that demonstrated such findings in remitted MDD (Green et al., 2013; Zahn et al., 2015). One explanation for this discrepancy is the employment of a shortened version of the VMST, further influenced by a smaller sample size compared to previous studies (Green et al., 2013; Zahn et al., 2015). It may also be due to the nature of the task, which assesses interpersonal self-blame rather blaming oneself for failure. The latter may be more relevant in the predominantly anxious MDD population selected for this trial. Previous studies using the VMST assessed remitted MDD patients contrary to the early treatment-resistant MDD population included in this study which created different selection biases as anxious distress patients are more likely to exhibit a chronic course and were therefore probably underrepresented in previous studies of fully remitted MDD. It is further suggested, that self-blaming biases may be a particular characteristic of the melancholic subtype of MDD rather than specific to other subtypes (Green et al., 2013; Zahn et al., 2015). Ultimately, the current findings highlight the need for developing additional experimental tasks to capture self-blaming biases in non-interpersonal contexts.

In chapter IV, I developed a novel task, the SAIT, that probed self-blaming emotional biases at the level of preceding events that may be perceived as the cause of negative social outcomes, to address questions raised by the previous chapter. The SAIT was used to investigate whether patients with MDD show self-blaming emotional biases and overgeneralised representations of preceding events when internalising blame.

The hypotheses were confirmed partly as the results demonstrated self-blaming emotional biases in the self-agency condition of the SAIT in the non-anxious MDD group, whereas MDD patients with anxious distress and HC participants did not show self-blaming emotional biases. Further, no change in self-blaming emotional biases post-intervention was detected in MDD patients with and without anxious distress who participated in the NeuroMood trial, irrespective of treatment group. Contrary to the hypothesis, patients with MDD did not show an overgeneralisation of preceding actions related to internalising blame relative to externalising blame on the SAIT.

The finding that MDD patients with anxious distress did not show self-blaming emotional biases confirms the results of the previous chapter that demonstrated that this patient group tends to externalise blame more than non-anxious MDD patients. As aforementioned, this finding is further supported by the clinical acknowledgement of irritability as a DSM diagnostic criterion for anxiety disorders, such as GAD or trauma-related disorders such as PTSD. Finding evidence of self-blaming emotional biases in the self-agency condition only, but not in the other-agency condition validates the task design which is constructed to evoke self-blame in the self-agency condition and blaming one's best friend in the other-agency condition (Green et al., 2013; Zahn et al., 2009). Failing to find a change in self-blaming emotional biases in the non-anxious MDD group post-treatment compared to baseline might have been due to low sample sizes in both intervention groups. Failing to find evidence for an overgeneralisation of negative preceding actions internalising or externalising blame, however, could also be due to potential weaknesses in the task design, such as, that the task may not have presented relatable social situations or may

have failed to offer relevant preceding events with a close causal relationship to the scenarios. This was despite best efforts to base its design on pre-study data.

Further, a task design that targets an unspecified or even disliked person instead of the participant's best friend might have been preferable, as participants reported to struggle in imagining that their best friend could act negatively towards them. Despite these challenges, participants were found to make meaningful choices in their responses, which argues for the SAIT's validity. Consequently, failing to find evidence for an overgeneralisation tendency might then indicate that most MDD patients are indeed able to make intact causal inferences regarding preceding events. In turn, this would suggest that self-blaming emotional biases must arise at a different cognitive level and are not due to difficulties in differentiated inferences regarding preceding events. This conclusion will require confirmation through further research in larger samples after optimising the SAIT further and potentially combined with qualitative research in order to provide further evidence of its validity. The most important modifications to the SAIT for such future studies, in my opinion, imply the generation of a closer causal relationship between preceding events and social situations based on the collection of further normative data.

V.1.3) Overall conclusion

The self-blame-targeted, self-guided psychological intervention with and without additional rtfMRI neurofeedback, developed for the NeuroMood trial, was found to be a safe approach to the treatment of current and insufficiently remitted, early treatment-resistant MDD. The clinical benefits of these interventions are comparable and resulted in a reduction of depressive symptoms

by 46% and response rates of more than 55% in both treatment groups. Although the influence of placebo-like effects cannot be excluded, it is likely that the engagement with self-guided psychological intervention components specifically contributed to beneficial effects. Differences appear to exist in the efficacy of these interventions for different MDD subtypes. MDD patients without anxious distress were found to respond better to the combined rtfMRI neurofeedback plus psychological intervention of self-blaming emotions.

It remains unclear whether higher levels of anger in MDD patients with anxious distress interfered with their treatment response to the rtfMRI neurofeedback and whether the rSATL-subgenual connectivity target might be less relevant for this MDD subtype. More research is needed to investigate these issues further, and future studies need to replicate the findings presented in this work. Future studies should control for non-specific effects. Given that the presented trial was lacking a treatment-as-usual group, a possible contribution of non-specific treatment effects to the improvement in both intervention groups cannot be excluded. Future studies should also investigate the long-term benefits of self-blame targeted rtfMRI neurofeedback and psychological interventions in MDD; a valuable endeavour that could contribute to developing novel treatment approaches for MDD patients who do not benefit from standard interventions.

A discrepancy between clinical and experimental measures of self-blaming emotions stress the need for developing novel tasks that assess self-blaming emotional biases in MDD in interpersonal and achievement-related contexts. It further highlights the importance of modifying existing measures to better capture the neurocognitive basis of self-blaming emotional biases in MDD.

Ultimately, the findings presented in this thesis are in partial support of the revised learned helplessness model in MDD. Interventions explicitly targeting self-blaming emotions in MDD were found to be associated with a significant improvement in depressive symptoms as well as self-esteem, which was particularly valid for non-anxious MDD patients who were found to present with self-blaming emotional biases on some, but not all measures. Finding evidence for the applicability of the revised learned helplessness model for MDD patients with anxious distress, however, appears to be rather challenging. There was experimental evidence contrary to the model's predictions in MDD patients of the anxious distress subtype by showing their increased levels of anger directed at others. Should future studies confirm the observation of these differences between anxious and non-anxious MDD, this might imply that a different theoretical and neural basis may underpin distinct subtypes of MDD. Ultimately this would suggest establishing differentiation in core themes in the treatment of specific MDD subtypes, in terms of neuromodulatory as well as psychotherapeutic approaches.

V.2) References

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Appendices

Appendix A: Phone screening template

Appendix B: Negative and positive stimuli for SAIT pre-study

Appendix A: Phone screening template

NeuroMooD Phone Screening Interview (Study 1/2)

Screening ID No: S____-_____

Instructions for Interviewer are marked in bold.

Text to be read literally is put into quotation marks and '*italic*'.

Oral consent to be read first:

This is the ethics approved wording which cannot be changed!

'I would like to do a short phone interview with you, which will take around 15 minutes. This is necessary to see whether some conditions rule out that we can include you into the study. You will be asked questions about psychiatric, neurological and medical symptoms, treatments, learning problems and whether such symptoms occurred in your family. I will also ask about substance or alcohol abuse. Things which are an obstacle to participate in MRI studies such as possible pregnancy or metallic objects will also be asked. Results of these questions will not be stored, but we ask your permission to store your contact information and whether you passed the screening for the study group in an electronic database which is protected by a password and can only be accessed by the investigators.'

I) General questions for all participants

Question	Response		Comments
Do you agree to this interview?	yes	no	If no => Exclusion
If participant's details have not been recorded prior to the phone screening, get full name & email address (do NOT note down here)			
Do you live in the Greater London Area?	yes	no	If no => where? How long does it take them to get to London?
How did you hear about our study?			
How many years of education have you had?			Towards the end of the study, controls will be selected to be age- and education- matched to the patient population
At what age did you start and leave school?			
What is your age?			If < 18 => Exclusion
Ask for participant's DOB ➔ record on separate piece of paper, not on this document!			
Are you right-handed?	yes	no	If no => Exclusion
Is English your first language?	yes	no	If no => Exclusion If any other early languages

			mentioned/foreign accent detected - Is English your parents' first language? At what age did you first speak English / did you learn English? Which language did you speak at home/school?
Have you ever been diagnosed with or treated for any psychiatric or psychological problem (e.g. Depression, Bipolar or manic-depressive, Anxiety, Panic Disorder, Posttraumatic Stress, Eating, Borderline Personality, Obsessive-Compulsive Disorder, Psychotic or schizophrenic disorders, Attention-Deficit-Disorder)?	yes	no	If yes => Exclusion as HC If yes => Who diagnosed? If more than 1 => Did they occur independently? Anxiety allowed in MDD if not prominent. If PD => screen for study2
Have you ever, at any time, taken anti-depressant or anti-psychotic medications (such as Prozac, Zoloft, Zyprexa, Haldol)?	yes	no	If yes => Exclusion as HC
Are you currently taking any medication?	yes	no	MDD/PD group: antidepressant medication allowed if on stable dosage for at least 6 weeks prior study participation. If other centrally active medications than antidepressants that will not be stopped anyway before participation for other reasons than study participation => Exclusion
If yes => What medications? Dosage? Since when this medication/dosage? <i>(must be on stable dose for at least 6weeks)</i>			
Have you been treated with counselling / CBT / psychotherapy in the past?	yes	no	If yes => When? How many sessions?
Are you currently treated with counselling / CBT / psychotherapy?	yes	no	If yes => Since When? How many sessions remaining? => Exclusion in case of CBT/psychotherapy; irregular sessions of counselling = ok / maybe inclusion after last session
Have you ever attempted suicide in the past?	yes	no	If yes => When? Para-suicidal act or clear intention?

			=> Exclusion
Have you ever been diagnosed with or treated for any neurological problem (weakness, gaze problems, walking problems, motor coordination, epilepsy, stroke, Parkinson's Disease)?	yes	no	If yes => Exclusion In case of concussions: for how long unconscious? Any signs on MRI?
Have you ever had a drug or alcohol problem?	yes	no	If questionable => Ask about any treatment for the problem. If yes => Exclusion
Have you ever had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?	yes	no	If yes => Explore further with question below
Have you ever taken any drugs more than once: for example stimulants, amphetamines, diet pills, cocaine, morphine, LSD, 'mushrooms', ecstasy, cannabis ('hash'), tranquilizers, steroids, sleeping pills or pain killers?	yes	no	If yes => Explore further: e.g. when drugs were last taken, how often; check if participant is likely to be drug free for study
In the past have you been intoxicated, high, or hungover from alcohol or drugs when you had other responsibilities (work, school, home) or did you have legal problems, problems with other people or accidents because of this?	yes	no	If yes or questionable => explore further; Ask for examples of behaviour, how frequently this occurred, any significant consequences? If significant => Exclusion
Have any of your first degree relatives (parents, siblings or children) ever been treated for/diagnosed with psychosis/schizophrenia/depression/bipolar disorder or manic depression?	yes	no	If yes => Exclusion as HC If yes => who treated for what?
Have you ever had any significant physical health problems, for example heart, lung problems, diabetes, hypertension, arterial diseases, thyroid function problems, liver, kidney disorders, rheumatoid disorders, infectious diseases or anything else? Do you still have your appendix? Have you ever had any surgeries in your life?	yes	no	If yes => check with Dr Zahn whether exclusion criterion Check with radiographers: thorax surgeries
Have you ever had any learning disabilities?	yes	no	If yes => Who diagnosed? Was your educational performance affected by this? Did you attend a specialist school? (If reading difficulty, check if able to read stimulus words at Visit 1)
Do you have hearing problems or problems with vision?	yes	no	If yes => Exclusion if cannot be corrected for experiment

Do you wear glasses or contact lenses?	yes	no	If yes => What prescription / strength? (Up to 7 diopters can be corrected in the scanner)
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II) Screening questions for all participants (Adapted MINI¹)

<p>Have you ever had a phase of at least 2 weeks in your life where you needed only a few hours (for example 3h) of sleep and were still totally alert and very active the whole day, where you were very enthusiastic and did things you usually wouldn't do?</p> <p>Have you ever had a period of time when you were feeling so good, "high", excited, or "on top of the world" that other people thought you were not your normal self?</p> <p>IF NO: Have you ever had a period of time when you were feeling irritable, angry, or short-tempered for most of the day, every day, for at least several days? What was this like? (Was that different from the way you usually are?) Was this outside of depression?</p> <p>⇒ IF YES: Did you also feel like you were "hyper" or "wired" and had an unusual amount of energy? Where you so much more active than is typical for you? (Did other people comment on how much you were doing?)</p>	<p>yes</p> <p>yes</p> <p>yes</p> <p>yes</p>	<p>no</p> <p>no</p> <p>no</p> <p>no</p>	<p>If yes => Exclusion</p>
<p>For the next question, please just say "yes" or "no", no details will be asked nor recorded:</p> <p>Have you ever been traumatized in a way, that you feared your life was in danger or were you sexually assaulted?</p>	<p>yes</p>	<p>no</p>	<p>If yes => Are you still bothered by it? If yes => Do you avoid anything (e.g. places/people) because of this? If currently significantly distressed => Exclusion</p>
<p>Do you experience frequent states of tension and use self-injuries such as cutting or burning to reduce tension?</p>	<p>yes</p>	<p>no</p>	<p>If currently yes => Exclusion If yes in the past: When the last time? Did this only occur during depressive phases? If occurred outside depressive phases => Exclusion</p>
<p>Do you get very tense or anxious, when your personal things (i.e. on your desk) are</p>	<p>yes</p>	<p>no</p>	<p>If yes => Did this only occur during depressive</p>

not symmetrically arranged, when you can't wash your hands, after you have touched a door knob, when you can't perform certain daily activities according to a fixed and detailed routine (e.g. washing, certain professional or household activities)?			phases? Does this interfere with your professional or personal life?
Have you ever heard voices with no person or audio-device as a source?	yes	no	If yes => Exclusion
Have you ever lost control of your body movements or your thoughts and felt controlled by an external power?	yes	no	If yes => Exclusion
Have you experienced unusual signs referring specifically to you and indicating great danger, for example by a group or person threatening your life?	yes	no	If yes => Exclusion

Have you ever been consistently depressed or down, most of the day, nearly every day, for at least 2 weeks?	yes	no	If yes => Exclusion as HC Check eligibility for MDD group: Ask when participant experienced those feelings & continue with section III (MDD group only)
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III) MDD group only

When has your most recent depressive phase started?	Exclusion: Duration of current MDE > 1 year		
When did you start to feel better again?			Does not need to report improvement over the course of the current episode, but no significant change over 6 weeks before randomisation!
Do you now feel as well as before your first depressive phase and do you feel back to your normal self?	yes	no	Only included if no and symptoms significantly distressing or interfering! If no: Ask => Do you experience symptoms that are distressing or interfering with your life?
In your most severe depressive phase, have you been consistently depressed or	yes	no	Only included if yes

down, most of the day, nearly every day, for at least 2 months?			
During the most severe period of that depressive episode, did you have a general loss of drive and energy, where your activities were either slowed down or only possible against a huge inner resistance?	yes	no	Only included if yes
During the most severe period of that depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up?	yes	no	Only included if yes

DSM-V criteria for MDD

Over the last month, has there been a period of time when you were feeling depressed, down, empty or hopeless? Was this most of the day, nearly every day?	yes	no	If yes: How long has this period lasted? As long as 2 weeks?
Over the last month, has there been a period of time when you lost interest or pleasure in things you usually enjoyed? Was this most of the day, nearly every day?	yes	no	If yes: How long has this period lasted? As long as 2 weeks?
During the same 2 week period: has your appetite decreased or increased nearly every day?	yes	no	
During the same 2 week period: have you been sleeping too much or too less nearly every day?	yes	no	If yes: How many hours more/less?
During the same 2 week period: have you been so fidgety or restless that you were unable to sit still? What about the opposite – talking more slowly than is normal for you? Has it been nearly every day?	yes yes	no no	If yes: Has it been so bad that other people noticed? Refers to observable psychomotor agitation/retardation, not merely subjective feelings(due to anxiety)
During the same 2 week period: have you felt tired or low in energy most of the day nearly every day?	yes	no	If yes: how bothering has it been?
During the same 2 week period: have you had feelings of worthlessness or excessive or inappropriate guilt nearly every day?	yes	no	Not merely self-reproach or guilt about being sick!
During the same 2 week period: have you had problems to think or concentrate or to make decisions? Has it been nearly every day?	yes	no	If yes: how bothering has it been?

IV) Study 1 only: Eligibility for MRI

For women: Are you absolutely sure that you are not pregnant?	yes	no	Exclusion for MRI if no
Do you use a contraceptive coil?	yes	no	If yes: Ask about brand/type Check MRI safety with CNS
Do you have permanent eyeliner or other permanent make-up?	yes	no	Potential exclusion for MRI if yes; tattoos can warm up, permanent make-up = definite exclusion! (=> also, tattoos may reduce MR image quality)
Any tattoos?			
Do you have loose dental implants such as fillings or crowns which cannot be removed before scanning?	yes	no	Absolute exclusion for MRI if yes
Do you have (fixed) metal/gold crowns or braces?	yes	no	Could cause MRI signal distortions
Do you have any implanted electrical devices? (pacemaker, brain stimulator, ear implants, implanted delivery pumps)	yes	no	Exclusion for MRI if yes
Could you have any metal in your body? (metal clips on the wall of a large artery, metallic prostheses including metal pins and rods, heart valves, shrapnel fragments)	yes	no	Exclusion for MRI if yes
Have you ever worked as a welder or metal worker? (this can lead to small metal fragments in the eye which you may be unaware of)	yes	no	Exclusion for MRI if yes
Do you get anxious in confined spaces?	yes	no	Exclusion for MRI if yes
Do you require a hearing aid?	yes	no	Exclusion for MRI if yes

V) Study 2 only: Panic Disorder group

Have you ever had an intense rush of anxiety, or what someone might call a 'panic attack' when you suddenly felt very frightened, or anxious or suddenly developed a lot of physical symptoms?	yes	no	If yes => Explore further with question below (=> and exclusion as HC)
How many panic attacks did you have?			
When did the last bout of panic attacks start?			
When did you start to feel better again?	Does not need to report improvement over the course of the current episode, but no		

			significant change over 6 weeks before randomisation.
Do you now feel as well as before your first panic attack and do you feel back to your normal self?	yes	no	Only included if no and symptoms significantly distressing or interfering! If no: Ask => Do you experience symptoms that are distressing or interfering with your life?
Has at least one of the attacks been followed by 1 month (or more) of persistent concern or worry about additional attacks or their consequences (e.g., losing control, having a heart attack, “going crazy”) or significant maladaptive change in behaviour related to the attacks (e.g., behaviours designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations)?	yes	no	If no => Exclusion If yes => Ask if they felt that way most of the time in this month.
Just before you began having panic attacks, were you taking any drugs, caffeine, diet pills, or other medicines?	yes	no	If yes => Explore further: Ask what they took exactly and in what dosage. How much coffee, tea, or caffeinated beverages do you drink a day? Exclusion if aetiological.
Just before the attacks, were you physically ill?	yes	no	If yes => Explore further: What did the doctors say Exclusion if aetiological (e.g. hyperthyroidism/cardiopulmonary disorders).
Do the panic attacks occur only in response to fearful situations, or only in response to phobic objects or situations, in response to obsessions, in response to reminders of traumatic events or in response to separation from attached figures?	yes	no	If yes => Exclusion (The disturbance may be better explained by another mental disorder, e.g. social anxiety disorder, OCD, PTSD or separation anxiety disorder)

Interview is stopped as soon as exclusion criterion is detected, the interviewer apologises for not being able to include the person and thanks again for the willingness to participate.

If necessary, one can explain that it is important for research studies to focus on specific types of depression (study 1) / panic disorder (study 2) because it is difficult to find significant results if patients with different types of depression or other problems are mixed together.

If person meets all inclusion/exclusion criteria for one of the study groups (MDD/Panic Disorder (PD)/ Healthy Control (HC)), contact information and study group are stored in password protected excel sheet.

The PIS and Consent Form for the respective study is sent to the person after screening and an appointment for Visit 1 is scheduled with at least 24h time after the person has received the PIS. The consent form is signed at Visit 1.

This sheet is reviewed after the phone interview, exclusion reasons are coded in separate sheet not linked with screening-ID, and the questionnaire is then shredded.

Comment:

The screening questions for major psychiatric disorders are based on clinical experience as providing high sensitivity and specificity for bipolar disorder, schizophrenia, OCD, PTSD and Borderline Personality Disorder. The screening questions for inclusion into MDD groups were taken from the melancholic subtype questions of the MINI/SCID for DSM-IV. This is because melancholic subtypes are most likely to fulfil ICD-10 severe depressive episode criteria and score high enough on the MADRS. Screening questions to exclude current MDD were taken from SCID for DSM-V, neglecting the DSM-V criterion of suicidal thoughts. Remitted MDD is defined as meeting no more than 3 diagnostic criteria for current MDD. Screening questions for Panic Disorder were taken from SCID for DSM-V.

- 1) Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H., Janavs, J. & Dunbar, G. C. (1997) *European Psychiatry* 12, 224-231.

Appendix B: Negative and positive stimuli for SAIT pre-study

	Negative Stimuli [self-agency] self-blame (guilt) <hr/> Imagine the following scenario:	Negative Stimuli [other-agency] other-blame (indignation) <hr/> Imagine the following scenario:
1.	You drive your best friend's car, cause an accident and damage it.	Your best friend drives your car, causes an accident and damages it.
2.	At your best friend's party, you spill wine on their carpet.	At your party, your best friend spills wine on your carpet.
3.	You speak negatively about your best friend to their boss.	Your best friend speaks negatively about you to your boss.
4.	After your best friend wins a competition, you spread nasty rumours about them.	After you win a competition, your best friend spreads nasty rumours about you.
5.	At a game's evening at your best friend's house, you cheat during a poker game.	At a game's evening at your house, your best friend cheats during a poker game.
6.	When babysitting for your best friend, you slap their child.	When babysitting for you, your best friend slaps your child.
7.	Your best friend lends you money, and you do not pay them back.	You lend your best friend money, and they do not pay you back.
8.	In front of strangers, you bring up one of your best friend's private memories.	In front of strangers, your best friend brings up one of your private memories.
9.	When talking about politics, you mock your best friend's opinions.	When talking about politics, your best friend mocks your opinions.
10.	In a meeting, you take all the credit for your best friend's effort.	In a meeting, your best friend takes all the credit for your effort.
11.	During an important exam, you copy from your best friend.	During an important exam, your best friend copies from you.
12.	You steal money from your best friend's wallet.	Your best friend steals money from your wallet.
13.	Whilst your best friend is on holiday, you kiss their partner.	Whilst you are away on holiday, your best friend kisses your partner.
14.	When with other friends, you tell one of your best friend's secrets.	When with other friends, your best friend tells one of your secrets.
15.	At a dinner party, you take your best friend's dessert.	At a dinner party, your best friend takes your dessert.
16.	After a double date, you criticise your best friend's choice of partner.	After a double date, your best friend criticises your choice of partner.
17.	On your best friend's birthday, you pretend to be ill to avoid attending their party.	On your birthday, your best friend pretends to be ill to avoid attending your party.

18.	To avoid seeing your best friend, you lie about your plans.	To avoid seeing you, your best friend lies about their plans.
19.	After too much alcohol, you shout at your best friend.	After too much alcohol, your best friend shouts at you.
20.	After noticing your phone is missing, you wrongly accuse your best friend of stealing it.	After noticing their phone is missing, your best friend wrongly accuses you of stealing it.
21.	At a party, you get food at the buffet for yourself, but not for your best friend.	At a party, your best friend gets food at the buffet for themselves, but not for you.
22.	You win the lottery and do not share any of the money with you him/her.	Your best friend wins the lottery and does not share any of the money with you.
23.	During a verbal fight, you push your best friend.	During a verbal fight, your best friend pushes you.
24.	During a disagreement, you swear at your best friend.	During a disagreement, your best friend swears at you.
25.	Behind your best friend's back, you tell their boss about their mistakes.	Behind your back, your best friend tells your boss about your mistakes.
26.	When your best friend rings the doorbell, you pretend not to be at home.	When you ring the doorbell, your best friend pretends not to be at home.
27.	You refuse to help your best friend move to their new house.	Your best friend refuses to help you move to your new house.
28.	When your best friend needs some help, you do not lend a hand.	When you need some help, your best friend does not lend a hand.
29.	After receiving a birthday present from your best friend, you do not thank them.	After receiving a birthday present from you, your best friend does not thank you.
30.	On the day of your best friend's birthday, you forget to say happy birthday.	On the day of your birthday, your best friend forgets to say happy birthday.

	Positive Stimuli [self-agency] self-praise (pride)	Positive Stimuli [other-agency] other-praise (gratitude)
	Imagine the following scenario:	Imagine the following scenario:
1.	Someone spreads a rumour about your best friend, and you defend you her/him.	Someone spreads a rumour about you, and your best friend defends you.
2.	When your best friend is ill, you leave a party early to look after them.	You are ill, and your best friend leaves a party early to look after you.
3.	Your best friend finds themselves	You find yourself homeless, and

	homeless, and you offer them a spare bed.	your best friend offers you a spare bed.
4.	Your best friend finds themselves unemployed, and you pay their debts.	You find yourself unemployed, and your best friend pays your debts.
5.	Your best friend needs a kidney transplant, and you donate yours to them.	You need a kidney transplant, and your best friend donates theirs to you.
6.	In a meeting, you let your best friend take credit for your work.	In a meeting, your best friend lets you take credit for their work.
7.	On a cold day, you give your best friend your coat.	On a cold day, your best friend gives you their coat.
8.	After the loss of a loved one, you comfort your best friend.	After the loss of a loved one, your best friend comforts you.
9.	In an accident your best friend falls into a lake, and you jump in to save them.	In an accident you fall into a lake, and your best friend jumps in to save you.
10.	After a long flight home, you pick your best friend up from the airport.	After a long flight home, your best friend picks you up from the airport.
11.	While your best friend is attending a funeral, you do all their housework for them.	While you are attending a funeral, your best friend does all your housework for you.
12.	When your best friend gets arrested, you pay their bail.	When you get arrested, your best friend pays your bail.
13.	You share your lunch with your best friend.	Your best friend shares their lunch with you.
14.	Your best friend is in a rush, and you offer them a lift.	You are in a rush, and your best friend offers you a lift.
15.	So that your best friend can visit their parents, you look after their pet dog.	So that you can visit your parents, your best friend looks after your pet dog.
16.	After your best friend gets their hair cut, you compliment their appearance.	After you get your hair cut, your best friend compliments your appearance.
17.	Your best friend falls over, and you help them to get up.	You fall over, and your best friend helps you to get up.
18.	Your best friend is worried, and you give them advice.	You are worried, and your best friend gives you advice.
19.	After your best friend is fired, you take them for dinner.	After you are fired, your best friend takes you for dinner.
20.	Your best friend loses their wallet on holiday, and you lend them some money.	You lose your wallet on holiday, and your best friend lends you some money.
21.	To give your best friend a night off, you look after their children.	To give you a night off, your best friend looks after your children.
22.	After your best friend breaks up with their partner, you commiserate with them.	After you break up with your partner, your best friend commiserates with you.

23.	Your best friend loses their job, and you listen as long as needed.	You lose your job, and your best friend listens as long as needed.
24.	After the death of your best friend's relative, you send a sympathy card.	After the death of your relative, your best friend sends a sympathy card.
25.	Your best friend is sad, and you console them.	You are sad, and your best friend consoles you.
26.	Your best friend is ill, and you go food shopping for them.	You are ill, and your best friend goes food shopping for you.
27.	Your best friend insults you, and you forgive them.	You insult your best friend, and they forgive you.
28.	You are crying, and your best friend gives you a tissue.	Your best friend is crying, and you give them a tissue.
29.	During your best friend's move to a new house, you offer to help.	During your move to a new house, your best friend offers to help.
30.	While your best friend is on holiday, you mow their lawn.	While you are on holiday, your best friend mows your lawn.